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THE BASIS OF SYMPTOMS

THE PRINCIPLES OF CLINICAL PATHOLOGY

BY

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AUTHORIZED TRANSLATION FROM
THE SEVENTH GERMAN EDITION BY

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THIRD AMERICAN EDITION

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TRANSLATOR'S PREFACE TO THE THIRD AMERICAN EDITION

THE translation into English of Professor Krehl's "Pathologische Physiologie" is closely identified with the name of Dr. Hewlett, who prepared the first two American editions of this work from the third and fourth German editions, respectively. It is with Dr. Hewlett's permission that I am offering to the profession a third American edition based upon the seventh edition of the German. Dr. Hewlett has also placed at my disposal whatever of his I have found available—a privilege I have freely used and for which I take great pleasure in acknowledging my indebtedness. The title of the earlier translations, Clinical Pathology, derived from the first German edition, has been continued, as a subtitle, in this volume, the new title, The Basis of Symptoms, having been selected to convey the immediate relation of the contents to clinical medicine.

Noteworthy advances have been recorded in the medical sciences since the publication of the second American edition. Thus, the last German edition in its growth reflects in particular the newer studies devoted to the cardiac arrhythmias; to the leukæmias and pseudoleukæmias; to such phases of infection and immunity as anaphylaxis, complement fixation and chemotherapy; to the phenomena of gastric secretion and motility; to the renal functional tests and the rôle of the incoagulable nitrogen; and, finally, to the glands of internal secretion, to gout, diabetes, fever, etc. In addition, there has been included a new chapter on "Constitutional Diseases and Diatheses."

The last few years have been significant also for the part which American science has contributed. There is scarcely a field in which cisatlantic workers are not creditably represented; while along many lines they are pioneers. I have made an effort to take cognizance of this fact, and have inserted many notes indicative of the same.

Particular attention has been devoted to the literature. Many of the older, and classical, German references have been omitted

and replaced by more recent studies, particularly when the latter are in the nature of collective monographs. The numerous American studies referred to in the text and footnotes contain, as a rule, comprehensive bibliographies.

Professor Krehl's appended note on the cardiac arrhythmias (referred to in his Preface) has been incorporated into the main body of the text.

The translation though not a literal one, does not depart in any essential way from the original text, and embodies, it is hoped, the spirit of the latter. I have allowed myself the privilege of certain condensations and slight rearrangements—all with the view of rendering the material more serviceable to the readers for whom it is intended. Editorial notes—several of which are taken from the earlier American editions—are included in parentheses.

It is with keen pleasure, finally, that I acknowledge my debt to Dr. R. G. Hoskins, Professor of Physiology in the Northwestern University Medical School, for his constant stimulus and many suggestions; and to Messrs. J. B. Lippincott Co. for their coöperation throughout the preparation of the volume.

ARTHUR F. BEIFELD.

CHICAGO, 1916.

AUTHOR'S PREFACE TO THE SEVENTH GERMAN EDITION

With a greater trepidation than ever, I commit this revision to the profession. In every department of pathological physiology there are diligent workers and the literature has grown immeasurably. My assistants, with whom it has been my pleasure to work, as well as Professor Schwenckenbecher, of Frankfurt, and Professor Morawitz, of Freiburg, have rendered me abundant aid, without which I should have found it quite impossible, even in small measure, to do justice to the wealth of material. Despite this, I cannot say, with any degree of certainty, that I am cognizant even of the more important work from German sources; while of foreign literature I have given only suggestions.

I am deeply sensible of my shortcomings, and I have seriously asked myself if the time has not arrived for a collaborative treatment of the contents of this volume; for it has attained a scope, which, unassisted, I can no longer hope to present evenly. There is not a chapter, indeed, which my colleagues could not have presented more ably.

Pathological physiology concerns the student, the teacher and the clinician. In our profession it is linked with the best we have in us, predicating thought and study and the desire to understand. I do not say that the speculative mind is essential to the proper conduct of medical practice; for success at the bedside is preeminently and fittingly the fruit of a full and cumulative experience. To him indeed, who would advise mankind, experience is all-important, but if this be the measure of his content, it is well. Let him pursue his way.

Our profession embraces something larger and finer, however; it is like a faith whose God may be judged from the character of him who worships. Thus to many comes the impulse to devote themselves with fervor to something purer, higher and less tangible; to ponder how the wondrous processes of life unfold themselves in the sick; to understand how disease arises out of health; to be a nature philosopher.

The tendency to speculate is deeply rooted in us of German

blood; to seize with winged thought what only calm, painstaking study can elaborate and acquire. We like to construct in thought edifices that can be erected only upon the foundation stones furnished by the more suitable and exact methods of the laboratory. And for each of us to have his own pathology still plays a prominent and, in my opinion, a not desirable rôle.

To curb this tendency and to foster a more definite leaning upon the biological sciences in general, is the desire of this volume and its purpose. Its justification lies perhaps in the attempt to correlate the functions of the different organs on a uniform biological basis; for despite their individuality, they are efficient only as parts of the larger whole. And to-day, more than ever, we are agreed that he who will understand disease must see clearly the interrelationship of all the organs—must consider the unit only in its bearing upon the ensemble.

For reasons beyond my control the publication of this book has been considerably delayed, so that when concluded, I would fain have made a number of alterations. This being impossible, I have appended a few notes on the cardiac arrhythmias.

References to the literature have been given with every possible care, yet I fear that many errors in volume and page citation have crept in.

L. KREHL.

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FOREWORD

THE remarkable development of pathologic anatomy during the past century was reflected in the clinical medicine of the time. Physical diagnosis reached its present plane of accuracy, the ability to predict the anatomic changes found at autopsy became the goal of certain clinical schools, and therapeutic nihilism became the order of the day since it was obvious that no medicine could have changed most of the alterations in structure that were found at autopsy. Modern surgery has indeed been able to cut many a Gordian knot prescribed by anatomic change; but modern medicine, though still directly dependent upon pathologic anatomy for the interpretation of many clinical syndromes, has turned its main path of development into other channels.

Anatomic changes do harm by interfering with certain functions of the body, but functional alterations may also be present without evident alterations of structure. The symptoms for which a patient seeks relief are all due to changes in function. Even when the physician cannot remove the anatomic cause of the disease, he may yet be able to alter the bodily functions in such a way as to relieve symptoms or other disease manifestations.

The functional outlook on disease requires from the physician that he think not in terms of diseased structure alone but also in terms of diseased physiology. The science of abnormal physiology is at present passing through a period of rapid development. It has been zealously studied in recent years by physiologists, experimental pathologists, biochemists, immunologists and by clinicians themselves. Modern pharmacology devotes itself mainly to the effect of drugs upon physiological processes. The bearing of this new knowledge upon the interpretation of clinical pictures and its application in the treatment of disease are to my mind the most important problems that lie before the modern clinical school.

In his book on Pathologische Physiologie, Ludolf Krehl has sought to interpret the various pictures observed in the clinic from the stand-point of disturbed physiology. That his work has met with wide approval is evident from the fact that it has passed through eight German editions and that it has been trans-

lated into a number of languages. The writer of this note is responsible for the first and second American editions, and it was with great pleasure that he learned of Dr. Beifeld's willingness to undertake a new American translation. To this new translation he wishes all success, not alone because such a work deserves success in itself but because success would indicate that our profession is taking an interest in the fundamental principles that underlie the modern development of internal medicine.

A. W. HEWLETT.

JANUARY, 1916.

DESCRIPTIVE NOTE

KNOWING its worth, I very gladly agreed to write a brief introductory preface to an American edition of Professor Krehl's well-known work. Not that it needs any words of commendation. A successful book in Germany, it has already been translated into several languages, and has long since passed beyond the probation stage; but a few words from me may serve to introduce it to the English-speaking profession. Those of us who were brought up on Williams's "Principles of Medicine" recall the pleasure and the profit derived from it, mingled now with the regret that we have no work of the same character to place in the hands of our senior students. This want Professor Krehl's book will supply. Herter's "Lectures on Chemical Pathology" cover part of the ground, and Cohnheim's well-known "Lectures on General Pathology" is somewhat similar. In Professor Krehl's work disease is studied as a perversion of physiological function, and the title "Clinical Pathology" expresses well the attempt which is made in it to fill the gap between empirical and scientific medicine. The facts presented are derived in part from studies upon patients, and in part from experiments upon animals, designed to explain clinical problems. The author has had the advantage of prolonged laboratory training, to which has been added that accurate knowledge of disease to be had only by years of study and teaching in the wards. For such a work as this there is at the present time great need. Every few years the laboratories seem to run ahead of the clinics, and it takes time before the facts of the one are fully appreciated by the other. In the complexity of the problems, sometimes in the fascination of the scientific side, we are apt to lose sight of the practical application to diagnosis and to treatment of the facts obtained in the laboratories. The surgeons have invaded the medical wards with great advantage to our patients, and in many diseases to the great improvement of the art of diagnosis. How helpful it would be if clinicians had always at hand skilled physiologists, pathologists, and chemists to apply their most advanced technic to clinical problems, and not the technic alone, but the biological and chemical principles upon

which medicine as an exact natural science is founded. Principles, as Plato reminds us, require constant revision and consideration; and this book, representing a revision to date of the "Principles of Clinical Pathology," will be most helpful to all students and teachers who wish to know the scientific basis of our art.

(From the Second Edition.) WILLIAM OSLER.

INTRODUCTION

THE different chapters of this volume are concerned with a consideration of the behavior of correlated organs under the influence of a particular disturbance of function. Intended as supplementary to texts on physiology and special pathological anatomy, the attempt is not made to cover what properly belongs to those fields. The arrangement of material is that conventional in the study of pathology in the German universities.

Conventional, too, is the treatment of the material—in part an anatomical, and in part a physiological consideration of disturbances in associated organs and functions. In this I am following also the current method of considering purely physiological processes. This clear, dispassionate, and to him who would know the phenomena of life, one might say sober, plan is a product of the newly arisen physiology of the last century. The new era was inaugurated with a mechanistic notion of the physical and chemical workings of the individual organs. Therein lay the tremendous advance of that transitional period—a change from the speculative to the empirical treatment of the subject.

Pathology underwent a like alteration; dyscrasias and diatheses were displaced by clearly defined organ-changes. This was the expression of the Virchow teaching, which associated each disease with a local pathology and acknowledged no generalized conditions. The pathological point of view, therefore, did not differ in any way from the physiological. But the lessons learned at the autopsy table fall far short of what we must know to understand the processes of life. In the failure to recognize this lay the weakness and the narrowness of that intense period.

What we have contributed to normal and pathological physiology in the effort to understand the life of the organs consists chiefly in the employment of more exact methods and in the recourse to physics and chemistry. How can the circulation be regarded other than from a mechanical point of view, or the digestion other than from the chemical or physico-chemical?

Pathology, in part then, is indeed only the normal under peculiar conditions, called morbid. The fault may reside in a constitutionally defective organ-correlation which leads to a dis-

turbance of function even under the ordinary conditions of life (endogenous causes); or noxious factors may arise outside the body (exogenous causes). Illustrative of the former is a congenitally weak heart muscle, and, of the latter, a mitral regurgitation on an infectious basis. In neither case can the owner of such a heart compete in muscular effort with normal men of his age and strength. In both, the circulation goes on under morbid influences, which can be studied and understood only from the point of view of physics, just as in normal conditions.

This is the guiding principle in the majority of processes dealt with by this volume. Disease is synonymous with a perverted function of cells, organs and organ-complexes. The cell is altered both in structure and in composition, or it is disturbed by nervous or chemical influences (hormones). The result in the average case is a functional deviation from the normal, and a limitation in vitality and efficiency.

An exhaustive treatment of our subject would demand not only a consideration of disordered cell function, but of the nature of its physical, chemical and morphological changes. In only a small minority of morbid conditions, however, has our knowledge progressed to that degree. In one case we know the function that is disturbed and the anatomical substratum; in another chiefly the chemical anomaly, and in a third we are familiar merely with certain functional abnormalities, the morphological or chemical basis of which are still dark.

Our knowledge of morbid processes depends primarily upon the stage of development of methods for their investigation. As this varies considerably in different disorders, our acquaintance with the pathology of individual organs is not uniform. This reflects the stamp of dominant personalities upon the lines of investigation pursued by their contemporaries. Controversies as to the proper point of view—whether functional, chemical or morphological—to be taken in the interpretation of the manifestations of disease have been, and to some extent still are, prevalent. The barrenness of such discussion is obvious, for these different aspects are closely bound together, granting that upon certain conditions a particular line of reasoning throws more light than another. Even so, under any circumstances, for a final judgment as to any pathological state, the problem must be viewed from every aspect.

Under pathological processes are included two essentially different types of events. The first is directly dependent upon the morbid factor itself; thus in sublimate nephritis, the injury to the renal epithelium may be looked upon as the immediate result of the passage through the kidneys of mercury in combination. The second type is exemplified in the dilatation of the left ventricle in aortic insufficiency—an event produced by the response of the organism to the valvular defect. Such a reaction represents an effort toward healing and is *per se* not pathological. In both a theoretical and a practical way these two types are diametrically opposed. Our effort, therefore, must be to place each manifestation of disease in one or the other of these categories, for such a distinction is of great importance in therapy. In practice, indeed, the tendency is to individualize too little.

In my opinion, then, there is but one correct way to study the majority of morbid processes and the functional disorders of the organs which produce them, and that is by a comprehensive comparison of physical and chemical anomalies in disease with conditions as we know them in health.

The scope of theoretical pathology is no more limited by a consideration of the disturbances that pertain to it than is that of the normal life processes by the study of the functions of the different organ-systems. The coördinate workings of the organs, their place in the scheme of the whole—and through this their efficiency—the structural and chemical building of the body from a single cell, the wonderful problems of heredity, adaptation, growth and death, the preservation of the characteristics of the species and the relation of mind to matter—these are questions which cannot be ignored if one wishes really to understand life. Each has its pathological aspect, and each is wonderful in itself. Some of these questions are touched upon in texts of general pathology. But the remainder await the worker who shall correlate our present knowledge.

These are all problems naturally of pathological physiology—problems which cannot be regarded as solved until their every phase shall have been illuminated. The desideratum includes the most comprehensive and difficult problems. In part they cannot even be systematized, because as yet we have penetrated too little into the fundamentals of normal biology. Even the general principles which we must adduce in the solution of these problems

are not, in all respects, clear. To attempt to solve them purely on a physical or chemical basis would be to build on false premises. A something, not unlike the long forgotten vitalistic doctrine, is manifest here, though it is a vitalism of a totally different character from that applicable to the consideration of organ disturbances.

But to what purpose all this here? To ask pardon because a pathological physiology begins with the circulation, and because in place of a well-rounded presentation only a picture here and there can be offered. And also to explain why the subdivisions of our subject fall into the well-worn tracks. We must dismember the processes occurring in each sick individual in order to group them for convenience of classification under disorders of particular organs. But in the living person, as the physician sees him, things are quite different; for at the bedside we must determine how a disturbance of the coördinate action of the different organs affects the individual as a whole.

THE BASIS OF SYMPTOMS

CHAPTER I

THE CIRCULATION

The Importance of the Circulation.—The circulation is of fundamental importance to the body. It is not, of course, true, as was formerly believed, that the functions of the individual organs depend primarily upon the amount of material that they receive from the blood. Without doubt their activities depend rather upon the condition of the parenchyma cells and upon the stimuli which these receive from hormones and from the nervous system. Yet it is certain that in warm-blooded animals, at least, a sufficient supply of oxygen, salts and food materials to the tissues is a necessary requisite for a normal course of life. Disturbances of the circulation are, therefore, of great importance, and the more complex the organ affected, the more serious are the results of such disturbances.

The Pulmonary, or Lesser, Circulation.—A disordered condition of the circulatory system may have its origin either in the pump which propels the blood or in the tubes through which the blood flows. The right ventricle drives venous blood at a comparatively low pressure through the pulmonary vessels, which form a system of short tubes whose combined area of cross-section is very great. Through the walls of the capillaries, the interchange of gases between the blood and the air in the lungs occurs; and since this interchange takes place quite rapidly, the pulmonary system of a large number of short tubes seems best adapted to the purpose. The vessels play a relatively subordinate part in controlling the circulation in the lungs, for the pulmonary arteries possess little, if any, tone.[1] So far as we know, the different parts of the lungs are functionally equal, and there would seem to be no necessity for a variation in the blood-supply to different pulmonary areas, though theoretically it might be highly desirable in morbid conditions of the lungs. During a period of rest, when only a slight interchange of gases is necessary, the rate of blood-flow in the lungs is comparatively slow; but during exercise, when larger amounts of gases must be inter-

changed, a great quantity of blood is propelled through the lungs. The increased respiratory movements assist the action of the heart in maintaining this more rapid circulation.

The Systemic, or Greater, Circulation.—The relations are quite different in the greater circulation. Here a higher blood-pressure prevails at the outset, its height depending upon the contractile strength of the left ventricle, and upon the size of the smaller arteries. Variable amounts of blood may be made to pass through different organs without any alteration of the general arterial pressure, for, as the resistance to the flow through one organ is lessened, the resistance through another may be correspondingly increased. Such a mechanism is of the greatest service, for here all parts are not of equal functional value as they are in the case of the lungs, and it may be necessary to furnish one organ with a rich supply of blood at one time, and then later to do the same for another. The activity of the muscle-fibres of the smaller arteries regulates the distribution of the blood without at the same time necessarily altering the general blood-pressure. Indeed, this latter must not sink below a certain point if the brain and eye are to perform their functions properly.

The flow of blood in the veins is caused in part by the slight blood-pressure transmitted through the capillaries from the arteries and in part by other forces. Among the latter are the suction exerted by the heart and the thoracic cavity, as well as the pumping effect produced by the varying pressure of the muscles and fasciæ upon those veins that are provided with valves.

The Heart

The Adaptability of the Heart.—Any of the various parts of the cardiovascular apparatus may be diseased without necessarily disturbing the general circulation. This is due to the fact that this apparatus, like so many others in the animal body, possesses a compensatory mechanism. The compensatory mechanism for pathological processes does not differ, however, from that which a healthy man possesses and uses in order to meet the varying physiological demands made upon the circulation.

The amount of work which the heart performs[2] may be approximately estimated if we know the volume of blood delivered at each systole, the velocity imparted to this

blood, the peripheral resistance and the number of heart-beats in a unit of time. In other words, it depends upon the size of the ventricular cavity in diastole, the number and intensity of the ventricular contractions and the degree of constriction of the blood-vessels. The latter, in the lesser circulation, depends primarily upon the condition of the lungs; whereas, in the greater circulation, it depends upon the condition of the smooth muscle-fibres of the arteries and upon the vasomotor nerves which supply them.

During the life of a healthy individual, the blood flows at varying rates of speed—rapidly when the cells need much oxygen or food material, slowly when this need is small. As stated above, it is possible that the blood supply to an organ, or possibly to several organs, should vary greatly without affecting the general blood-flow. This is brought about by a contraction in one set of vessels, compensating for a dilatation in another set. Yet this compensation cannot meet all emergencies on account of the limited quantity of blood in the body. When large amounts of blood are needed in several parts of the body at the same time, they can be furnished only by increasing the velocity of the general blood-stream.

We might think that propelling a larger amount of blood would not necessarily increase the work of the heart, for, as the volume of blood increased, the general blood-pressure might be so decreased that the two would counterbalance each other. As a matter of fact, however, this does not occur, and, indeed, could not occur, on account of the relations that exist between the amount of blood propelled, the general pressure and the rate of flow. For example, if an extra supply of blood to the body were necessary, a diminution in the general arterial pressure would so reduce the difference in pressure between the arteries and the veins that the rate of flow in the capillaries would be insufficient to keep the heart supplied with fresh blood. Thus it is that any great increase in the rate of flow is incompatible with a lessened arterial pressure, and that consequently such an increased flow necessarily entails more work for the heart.

The work of the heart may be increased in another way, viz., by increasing the peripheral resistance. The latter varies frequently and considerably even in health, for we know that the irritation of numerous

sensory nerves will call forth contractions of the smaller arteries and therewith increased resistance. It is theoretically possible that this increased resistance should be overcome without additional work for the heart, provided that as the resistance is increased, the amount of blood delivered is correspondingly decreased. Such a condition, however, would slow the circulation to such an extent that the body could not perform its functions properly; and, as a matter of fact, it does not occur. We may say, therefore, that any marked increase in the peripheral resistance necessitates more work for the heart.

The heart is, as a matter of fact, the best motor known to man. It performs equally well the small amount of work necessary when a man is at complete rest, and the large amount called forth by great exertion. It possesses, therefore, the power of adapting itself to the varying demands made upon it. Not every man's heart is capable of the most extreme exertion, and "a tailor in a large city could hardly furnish the circulation necessary for the ascent of the Matterhorn." The weight of the muscular tissue of the heart—and with this its capabilities—bears a certain relation to the weight of the skeletal muscles. The tailor is unable to ascend the mountain mainly because his general musculature is weak. If this be improved by training, the heart also increases in its capabilities, and usually at a more rapid rate. Indeed, a healthy heart rarely fails in any effort. It possesses extreme adaptability, and, what is of greater importance, the adaptation occurs precisely at the time when most needed. To this fact the body owes its remarkable capacity for work. For example, when a ventricle in diastole becomes unusually filled (even up to six times its customary capacity),[3] the next systole, though it may not drive out all the blood, propels at least several times the ordinary quantity. Furthermore, if the arterial resistance be suddenly increased, it is as promptly overcome by the succeeding ventricular contractions. There is no time lost in experimentation: the demand and the accomplishment occur together.[4] This wonderful adaptability of the heart expresses itself both in its powers of dilatation and of contraction. Thus in diastole the ventricles will readily expand and take up greater amounts of blood without a corresponding increase in their ten-

sion. Only a slight pressure is necessary to distend the heart after the first short period of suction is passed.[5] When the ventricle is nearly filled, however, the tension rapidly increases. The same occurs even though much larger amounts of blood must flow into the heart during each diastole. The elasticity of the heart-muscle, which governs the resistance to the inflowing blood, must, therefore, vary with the amount of fluid that is to enter. By means of this variation it is possible for the ventricle to receive very different amounts of blood within the same period of time.

The contractility of the heart likewise bears a certain relation to the amount of blood to be propelled: it also accommodates itself to the increased demand. The ventricle is able, therefore, to expel almost completely much more blood than usual, and this even against greatly increased resistance.

This remarkable adaptability is usually regarded as a function of the muscle itself;[6] for the ventricular apex possesses the above properties to precisely the same degree as does the intact organ.[7] To those who regard the few nerve fibres and ganglion cells in the apex as possessing not only conducting but other higher powers, this view may be unsatisfactory. At any rate, the actual cause of the accommodation is no better understood than is that of the automatic beat of the heart; while additional complexities have been introduced by the important studies on the structure of the conduction system.

So far as we know, the heart uses all its muscle-fibres at each contraction. The increased work, therefore, is accomplished not by calling new fibres into play, but by causing the old to contract more quickly and more energetically. How is this brought about? In a skeletal muscle, poisoned by curare, the strength of the contraction depends not only upon the stimulus but upon the weight to be lifted. If we ascribe similar properties to the heart muscle, we are led to the conclusion that the amount of distention directly regulates the force of the subsequent contraction. v. Frey rightly remarks that the response occurs too quickly to be a reflex act. "It frequently happens that the heart does not feel the increased resistance until the beginning of systole. It is then too late for a reflex adjustment, and, if it waited for that, the next contraction would be abortive. Experience, however, shows that

this is not the case; indeed, the contractions which follow immediately after an increased call upon the heart are, as a rule, unusually powerful."

Although the nervous system is not necessary for this adaptation, yet it would seem that in many cases both the elasticity and the contractility may be increased by nervous influences. Kauders[8] has performed a remarkable series of experiments, in which he has shown that an increased resistance, produced by an irritation of a sensory nerve —the sciatic, for example—is better overcome by the left ventricle than the same degree of resistance produced by direct compression of the aorta. In the latter case, the left ventricle failed to do its work, and the pressure in the left auricle increased; whereas in the former, the work was not only well done, but the auricular pressure was even diminished. The left ventricle worked here to better purpose, probably because it was favored by nervous influences from the medulla.

As has been shown above, when the peripheral resistance is increased, or when there is a demand for a greater blood supply, the heart can meet the new requirements only by doing more work. The slightly lengthened systole, which may occur under these circumstances, and which amounts to not more than from twenty to thirty per cent., does not lessen the work sufficiently to compensate for the other factors.

The heart's capacity for work is indeed very great. Even though, experimentally, the amount of blood in the ventricles during diastole be increased sixfold, they are able to empty themselves almost completely; and a doubling of the arterial pressure does not cause serious embarrassment. Yet, on the other hand, an increase in the heart's activities is not without its disadvantages. For, in the first place, the increased work is made possible only by increasing the chemical decompositions in its muscle; and, in the second, an excessive rise in arterial pressure is by no means without danger, especially if the blood-vessels are not perfectly healthy.

Hypertrophy of the Heart.—Frequent and marked increase in the work of the heart leads to secondary changes. In this respect, so far as we know, the heart acts precisely like a striated muscle. Continued exertion leads to its enlargement, owing to the increase in size and number of its muscle-fibres.

It then reaches a new equilibrium and is able to accomplish without effort tasks that formerly called its reserve force into play. Bauer designates this as a "strengthening of the heart."[9] When an increased effort is demanded of it, the work is divided among more numerous and stronger fibres, and it is therefore more easily performed. The extreme limits of accommodation have also become greater, for we may assume that the stronger hypertrophied muscle possesses a greater reserve force than the former weak muscle; and experience seems to bear out this assumption.

If the weight of the heart muscle depends upon the amount of work done, we should expect that the weight would vary in different individuals.[10] In the numerous and careful observations of W. Müller[11] and of Hirsch,[12] such a variation has been demonstrated, there being a definite ratio between the weight of the heart and the total weight of living body tissue, though this is not always the case, especially in youth.[13] We have no method of directly determining the amount of work that has been performed by a heart. Perhaps it would be of value to know the work done by the body as a whole, although different sorts of work affect the circulation differently. It is also difficult to determine the total weight of living tissue in a body, or even that of the muscular system, which is of special importance. Thus far, statistics have dealt with the relation that exists between the weight of the heart and the total body weight; and although the latter introduces inaccuracies on account of the varying amount of fat and the presence of œdema, nevertheless the figures from a large amount of material have shown that the ratio between the weight of the heart and that of the body varies only within narrow limits, from which Hirsch concludes that the activity and weight of the body musculature exercise a determining influence upon the weight of the heart.

If this ratio of the weight of the heart to the body weight be increased, we speak of an hypertrophy of the heart. Although such an hypertrophy may arise from a variety of causes, it is questionable whether it ever results from prolonged exertion alone. We know that severe muscular exertion increases the weight of the heart, for the amount of the blood to be propelled is much greater than normal

and the arterial pressure is not diminished, but is usually increased.[14] Under these circumstances, the heart necessarily becomes larger, but this increase in size is usually not out of proportion to the accompanying increase in the skeletal musculature. In other words, the relation existing between the heart-muscle and the skeletal muscle is undisturbed, and in this sense no hypertrophy arises. We possess no very exact anatomical observations on the size of the heart under such conditions. Clinical examination, however, usually fails to show any hypertrophy. Yet some observations speak in favor of the view that hypertrophy without weakness may result from prolonged over-exertion; and the orthodiagraphic method of examination bears out this conception.[15] Race-horses possess relatively large hearts, prolonged exertion increases the weight of young dogs' hearts to a relatively greater extent than it increases the weight of their muscles,[16] and skee-runners of Denmark, who were apparently healthy, have been shown in several instances to have hypertrophy of the left ventricle. We may say, nevertheless, that a relative increase in the weight of the heart as a result of over-exertion is a great rarity, and that when it occurs it is usually due to pathological changes in the muscle. We shall return to this subject in speaking of heart hypertrophy.

The specialized muscle fibres forming the cardiac conduction system do not participate in the hypertrophy of the ordinary heart-muscle.

Valvular Disease of the Heart.—As has been said, the heart possesses the power of adjusting itself to varying circulatory conditions which would otherwise interfere seriously with the supply of blood to the body. It exercises this power not only to meet the varying demands made upon it during health, but to compensate for the destructive processes wrought by disease.

The function of the valves of the heart[17] is to direct the current of blood in the proper direction. In order to prevent leaks, the valves must be intact, they must be properly controlled by the papillary muscles and the chordæ tendineæ, while the openings which they close must be reduced in size by the contraction of the surrounding ring of muscle—a most important factor. The orifices of the heart become much smaller during systole, at which time they may be readily closed; whereas during diastole they are relatively too large for the valves.

The Etiology of Valvular Disease.—Diseases of the valve segments may be produced by micro-organisms or their toxins.[18] Acute articular rheumatism and the septic diseases are the most frequent causes; next to these we may name typhoid fever, scarlet fever, variola, chorea and gonorrhœa. Indeed any infectious disease may injure the heart valves and the heart muscle as well.

The bacteria most frequently found in acute endocarditis are the streptococci, staphylococci and pneumococci, although other organisms, as the gonococci, are occasionally present. In a number of instances, as in gonorrhœal endocarditis, the heart is simply one localizing point of a general infection. In other cases, as in the acute exanthemata, the heart complications are to be regarded as the result of secondary infections. The original disease prepares the ground for the invasion of the organisms which attack the heart valves.

Not infrequently, however, no bacteria are found in the endocardial vegetations. It is possible in such instances that organisms have been present, but that they have died out, or, on the other hand, that the condition may have been produced not by the local action of micro-organisms, but by toxins generated in some other part of the body. No micro-organisms are found, as a rule, in the endocarditides complicating carcinoma, tuberculosis or nephritis. Not infrequently none has been found in the rheumatic endocarditis, though from other cases of this disease various bacteria have been isolated. The real cause of the heart complications of rheumatism is of considerable interest, for rheumatism is analogous in many ways to an infection with pyogenic cocci[19] (see p. 153).

Infections may attack different parts of the heart, certain ones showing a tendency to localize on the valves, others to involve more especially the myocardium. The injury to the valves begins with a degeneration of the endothelium, quickly followed by a deposit of blood-platelets and by thrombi. The tissue reaction comes later, and is more marked when the auriculoventricular valves are affected than when the semilunar valves are diseased.

It is not our purpose to discuss the different anatomical and clinical forms of endocarditis. Suffice it to say that by ulceration and shrinkage the valves may be shortened or perforated, and that by adhesions along their margins the orifices may be nar-

rowed. Furthermore, owing to a concomitant myocardial affection, the orifices may not be properly closed during systole, or the auriculoventricular valves may not be efficiently controlled by the chordæ tendineæ. These latter factors are of no little importance. For example, when at autopsy we see only a slight marginal affection of the mitral leaflets, whereas during life there had been a decided functional insufficiency, we must regard the complicating myocarditis rather than the valve lesion as the cause of the disturbances in functions. No one who understands the closure of the auriculoventricular orifices can believe that such a minimal affection of the valve could possibly be the sole cause of a serious insufficiency. It is an interesting fact that the endocarditides complicating ulcerating carcinomata and tuberculosis are much less frequently diagnosed than are those complicating rheumatism. Since a myocarditis is usually absent in these cases, the muscular rings contract well during systole, and the heart is less likely to be rendered insufficient from the valvular affection.

Chronic endarteritis is another important factor in the production of valvular disease. This usually spreads from the aorta to the valves, though it may arise primarily in the intima of the valvular vessels. The great significance of syphilitic processes at the root of the aorta in the causation of aortic insufficiency is fully recognized to-day.[20]

Finally, the insufficiency may develop because the valves or chordæ tendinæ are torn during very severe exertion, as the result of a great rise in intracardiac pressure—a very uncommon accident.[21]

The large thrombi which are sometimes found in the left auricle may hinder the flow of blood, and even produce the symptoms of a mitral stenosis. The clinical signs and symptoms so produced are not as yet well understood.

The effects of valvular lesions may show themselves in two different ways—either the orifices are not properly closed when they should be (insufficiency), or they cannot be opened widely enough to allow the blood to pass through freely (stenosis). Whether, in a given case, the one or the other occurs—or, as frequently happens, both occur together—depends upon the nature of the anatomical changes present.

The seat of the disease is in part dependent

upon the causative factor. Arteriosclerotic lesions most frequently affect the left semilunar valves on account of their proximity to the aorta. As a rule, a fresh endocarditis will produce an insufficiency and not a stenosis. The valvular vegetations in conjunction with the diseased heart muscle render the closure of the valves imperfect; whereas in order to produce a stenosis, a chronic inflammation with ultimate adhesions between the valve leaflets is necessary. The grade of insufficiency, or of stenosis, *i.e.*, the amount of blood which in the former case flows back, and in the latter is hindered from passing through the orifice, is determined partly by the condition of the heart muscle and partly by the anatomical changes in the valves.

Muscular Insufficiency.—We have already mentioned the great importance of a proper constriction of the valvular orifices during systole by the surrounding ring of muscular tissue. A faulty constriction may entail serious consequences, and the so-called muscular insufficiencies are much more common than is generally supposed.[22] They occur most frequently as a result of myocardial disease; and, in chronic myocarditis, especially, they may lead to precisely the same disturbances of function as does a shortening of the valve segments. Indeed, the diagnosis between the two is often extraordinarily difficult; and many reported instances of "healed valvular disease" are doubtless merely improved cases of myocarditis with muscular insufficiency.

Muscular insufficiencies occur much more frequently at the auriculoventricular orifices than at the semilunar openings. At the mitral orifice they are usually due to a faulty contraction of the surrounding ring of muscle, or possibly at times to a lack of control of the valve segments by the papillary muscles and chordæ tendineæ. On the right side of the heart the contraction of the ventricle, as a whole, is usually at fault. According to v. Jürgensen, the slow contraction of the fatigued muscle may also interfere with the closure of the valves. The term relative insufficiency has been used for the condition in which the orifice is so widened that the valves are no longer able to close it. Although this stretching of the opening may, indeed, occur, we must insist that, after all, the essential factor is not the dilatation of the ring, but the faulty constriction during systole.

A relative insufficiency of the valves at the entrance to the aorta is much less common. At times it is due to an insufficient development of the muscle just beneath the semilunar valves; or it may originate in a dilatation of the fibrous ring at the beginning of the aorta.

Aortic Insufficiency.—It is now necessary to point out how the various valvular lesions affect the distribution of the blood in the body, and how the heart accommodates itself to the new conditions arising from the valvular defects.

When there is an insufficiency of the aortic valves, a part of the blood that is thrown into the aorta by the contraction of the left ventricle is returned into that cavity during diastole. The amount that flows back is determined by the size of the pathological opening left by the improper closure of the valves, by the difference between the pressure in the aorta and that in the ventricle, and by the duration of diastole. An increased heart-rate, which shortens more especially the diastolic period, should be of advantage in aortic insufficiency, since it lessens the amount of the leak backward.[23] Clinically, a rapid heart action is not infrequently found associated with this lesion, but we are ignorant of its cause. The walls of the ventricle are very flabby during diastole, so that they are easily stretched by the stream of blood flowing in under high pressure from the aorta. This leads to a dilatation of the ventricular cavity, the amount of dilatation depending upon the quantity of blood which flows back and upon the degree of elasticity of the muscle wall. In early diastole the ventricular wall is particularly flabby, but as the filling proceeds, it becomes more tense, while toward the end of diastole the tension increases rapidly. By thus increasing the resistance to the inflowing blood the ventricle can protect itself against overdistention.[24] We have already seen that this resistance varies normally with the varying amounts of blood which must be delivered, and that the ventricular wall becomes more distensible whenever larger quantities of blood must be propelled (p. 5). The abnormal filling of the ventricle in aortic insufficiency may or may not act as a hindrance to the entrance of blood from the auricle. Whether the one or the other occurs depends mainly upon this variation in the elasticity of the ventricular musculature. If distention and elasticity go hand in hand in order to accommodate the extra amount of blood,

it is possible that the auricle will empty itself as usual and that there will be no disturbance in the flow of blood from the lungs. Such cases do occur, and have been observed both clinically and experimentally.

On the other hand, many patients with aortic insufficiency show symptoms referable to a damming back of blood into the lungs. Their dyspnœa and the marked accentuation of the pulmonic second sound are indicative of increased pressure in the pulmonary circulation. It is easy to understand how this might be brought about by an uncomplicated aortic regurgitation; it is only necessary for the tension of the ventricular wall to increase before all the blood from the lungs has entered the ventricle. This would hinder the entrance of blood from the auricle and would tend to produce a pulmonary congestion. Furthermore, the suction of blood from the lungs due to the expansion of the ventricle in early diastole may also be diminished owing to the stream entering from the aorta. We have both clinical and experimental evidence that under such circumstances a pure aortic regurgitation may cause a stasis of blood in the lungs.[25]

In spite of its increased contents, the left ventricle in aortic regurgitation empties itself in about the same length of time as does the normal ventricle, although according to recent observations[26] it may not empty itself so completely. For there is evidence that the blood is not usually entirely expelled during systole if the ventricular cavity be greatly dilated. This fact, however, is really of no great importance in the matter under consideration, for so long as the ventricular muscle is efficient, the residue of blood left in the cavity at the end of systole is insignificant compared with that which streams back from the aorta during diastole.

In a series of classical experiments, Rosenbach[27] has shown that after artificially puncturing the aortic valves of a dog, all the symptoms of an insufficiency occur without any marked lowering of the mean arterial pressure. This experiment has been frequently repeated, but with varying results. In rabbits, the mean pressure is usually lowered as a result of the operation, whereas in dogs it may remain normal, be lowered or even be raised. These variable results probably depend, in the first place, upon the strength of the heart, and, in the second place, upon the severity of the lesion. The rabbit's weak heart cannot so readily

compensate for the injury, and its blood-pressure sinks. The dog's stronger heart readily overcomes a slight injury (*e.g.*, puncture of the valve by a rod); whereas a more serious one (*e.g.*, tearing off a valve) results in a lowered mean blood-pressure. It is possible that nervous reflexes may play some part in maintaining the blood-pressure in these cases, especially when the injury to the valves is sudden. The principal factor, however, is undoubtedly the accommodation of the heart-muscle itself.

In man, moderate and severe cases of aortic insufficiency are generally associated with a very considerable pulse-pressure, evidenced by an augmented systolic and a diminished diastolic pressure.[28]

All our experience goes to prove that a muscle will hypertrophy if it does an increased amount of work over a long period of time. We should expect the same rule to apply to individual parts of the heart, especially since their work is not limited to eight or ten hours a day, but is continuous, day and night. The work of the left ventricle is increased in aortic insufficiency, for it must propel not only the blood which enters from the auricle, but, in addition, that which leaks back from the aorta during each diastole. The total amount expelled is therefore increased, while the pressure against which it is expelled is but little changed. Practical observations have shown that in aortic insufficiency there is always an hypertrophy of the left ventricle with a dilatation of its cavity. The cavity is dilated on account of the abnormal amount of blood which it must accommodate, and the walls hypertrophy because of the extra work thrown upon them. If the conditions for an increased pressure in the left auricle, as described above (p. 13), are present, then its work and the work of the right ventricle are also increased, and hypertrophy of these two parts of the heart results.

Unfortunately we possess no exact anatomical data concerning these last points. The thickness of the heart wall at autopsy is greatly influenced by the condition of the heart when it stopped beating, whether it was in systole or diastole, so that we cannot judge from such measurements as to whether such slight hypertrophy as would occur in the left auricle and the right ventricle in cases of aortic insufficiency was present or not. Perhaps the

employment of W. Müller's [20] method will throw more light on the subject.

It is often erroneously stated that every aortic insufficiency is accompanied by a considerable, and easily demonstrable, enlargement of the left ventricle. When the muscle is efficient, the degree of dilatation and hypertrophy is directly dependent upon the amount of blood which regurgitates from the aorta. If a third or fourth of the volume driven out leaks back, it is possible that the lesion can readily be diagnosed clinically from the characteristic murmur, but that the hypertrophy and dilatation of the left ventricle will be so slight as to elude the ordinary methods of physical examination.

Aortic Stenosis.—In stenosis of the aortic orifice the flow of blood from the left ventricle into the aorta is impeded. It is probable that even under physiological conditions this orifice is not round and large during systole, but that it is encroached upon by the contraction of the muscle which surrounds it and which is an extension upward of the ventricular musculature. The blood flows smoothly up to the contracted portion and then out into the wider aorta. Under ordinary conditions, the delicate semilunar valves are easily thrust aside. If, on account of disease, they become stiff and rigid, they hinder the escape of blood more or less. The ventricle must, therefore, work against a greater resistance. The prolongation of the ventricular systole, which may be from seven to thirty per cent.[30] longer than normal, is by no means proportionate to the increased resistance. The lesion, therefore, causes a greater amount of work to be thrown on the left ventricle. As a result of this extra work, we always find an hypertrophied left ventricle in cases of aortic stenosis. At first, there is no dilatation of its cavity, and the auricle, lungs and right heart are entirely unaffected. A dilatation will occur only when the heart muscle can no longer accomplish the additional work, either because the obstruction has become too great, or because the muscle itself is weakened.

Mitral Stenosis.—Lesions at the mitral orifice produce more complicated conditions than do those at the aortic, because they lead to changes in the lungs and in the right heart.

In mitral stenosis [31] there is a hindrance to the flow of blood from the left auricle into the left ventricle. When the

auricle contracts, it must overcome a greater resistance, and this additional work leads to an hypertrophy of its musculature.. On account of the thin walls, however, its capacity for increased work is very limited, so that a dilatation occurs much earlier than in the case of the ventricle. An important factor contributing to this dilatation is the increased pressure which prevails in the pulmonary veins. At each systole of the auricle, an unusual proportion of its contents is forced back into the pulmonary veins owing to the obstruction in front at the mitral orifice. During diastole, therefore, the blood from the lungs enters the auricle with more than ordinary force, the diastolic pressure in the auricle is increased, and, owing to the diminished muscular tonus during this period, the cavity becomes dilated.

The abnormal pressure in the pulmonary veins is transmitted through the short and relatively wide capillaries of the lungs to the pulmonary artery. Everything now depends upon the behavior of the right ventricle, which is placed in much the same position as is the left ventricle in a case of aortic stenosis. The pressure in the pulmonary artery must be maintained at a higher level than usual, in order to conserve the difference in pressure between the artery and vein, and, in turn, the flow of blood through the lungs. We recognize this increased pulmonary pressure, clinically, by the accentuation of the pulmonic second sound. The extra work necessitated by this high pressure is thrown upon the right ventricle and leads to its hypertrophy.

The effect of mitral stenosis upon the left ventricle[32] depends entirely upon the amount of blood that the latter receives. When the stenosis is slight and the right heart maintains the necessary pressure in the pulmonary system, the left ventricle is not affected, for it receives its customary supply of blood. If, however, the right heart cannot compensate for the obstruction present, then the left ventricle is not filled to the normal amount, its work is diminished and its muscle atrophies. This reasoning has been confirmed by the findings at autopsy. In pure mitral stenosis, the left ventricle is either normal or atrophied. If at times an hypertrophy of the left ventricle has been found, it is to be attributed to an associated mitral insufficiency of simultaneous

or previous origin. The two lesions are very frequently combined, and this naturally modifies the resulting anatomical changes.

Mitral Insufficiency.—The conditions present in mitral insufficiency are very similar to those in mitral stenosis. A part of the contents of the left ventricle is thrown back into the auricle during systole, and the degree of insufficiency may be measured by the amount of blood which takes this backward course. The lungs and the right heart are affected precisely as in the case of mitral stenosis. The left auricle becomes dilated and hypertrophied, and the blood-pressure in the pulmonary system is raised. The work of the right ventricle is increased by the heightened pulmonary pressure; whereas it tends to be lessened by the diminished amount of blood that comes to it, and consequently by the lessened systolic output. Ordinarily the effect of the increased pulmonic pressure predominates, and we find an accentuated pulmonic second sound and at autopsy an hypertrophied right ventricle. Sometimes these are not present, and we may then assume that the left auricle dilates at each ventricular contraction to receive the regurgitated blood and that it empties itself during its systole, thereby compensating in a measure for the mitral defect. Such favorable conditions could only occur in the milder grades of insufficiency.[33]

During diastole the blood flows into the left ventricle with unusual force, owing to the increased pressure in the auricle and the pulmonary veins. There is also more blood to flow in on account of the overfilling of the left auricle and the pulmonary system with regurgitated blood. A certain amount of blood, varying according to the grade of insufficiency, moves back and forth at each beat between the left ventricle on the one hand, and the left auricle and pulmonary blood-vessels on the other. The ventricle, therefore, pumps more blood than usual, which we have no reason to believe that it does against a lessened resistance, for the mitral leak is hardly large enough to bring that about. The increased work performed by the left ventricle leads to its hypertrophy, a condition always present in mitral insufficiency.[34] The ventricular cavity also becomes dilated owing to the larger quantity of blood which it receives during diastole. Thus, hypertrophy and dilatation of the left ventricle go hand in hand. This com-

bination is of advantage not only in propelling the blood, but probably also in withdrawing it from the auricle and from the lungs during diastole.

Valvular Lesions of the Right Side of the Heart.—Valvular lesions of the right side of the heart give rise to secondary changes very similar to those which take place on the left side under corresponding conditions. We must remember, however, that the musculature of the right ventricle is relatively weak, and that it is not capable of the same degree of accommodation as is that of the left ventricle; furthermore, that there is no powerful ventricle directly behind the tricuspid orifice to compensate for its disabilities. Valvular lesions of the right side of the heart are characterized by the fact that they develop almost exclusively during the fetal period. Although the tricuspid valve is but rarely the seat of a verrucous inflammation in later life, a relative insufficiency of the tricuspid orifice is no uncommon sequel to valvular disease of the left heart.[35] Disease of the pulmonary valve, developing during adult life, is a great rarity.

During fetal life, micro-organisms in the blood-stream usually injure the valves of the right side of the heart, whereas in extra-uterine life those of the left side are the ones which are more frequently affected. One is tempted to explain this remarkable fact by the relative amounts of work done by the two sides or by the influence of the aërated blood, since in fetal life it is the right side which receives the oxygenated blood. We have no proof, however, for either of these two hypotheses. A fetal endocarditis is not uncommonly associated with congenital malformations, such as septum defects, transposition of the arteries or persistence of the ductus Botalli.[36] Possibly the malformations are primary and tend to diminish the resistance of the endocardium to infectious agents. This hypothesis would at least be the most natural explanation of their almost exclusive predilection for the right heart. The most important of the congenital heart lesions is pulmonary stenosis. This anomaly, which may be situated in the neighborhood of the valves, or at the conus arteriosus, leads to hypertrophy of the right ventricle precisely as does an aortic stenosis to hypertrophy of the left. Of the purely developmental anomalies only defects in the ventricular

septum are frequent; in these a systolic murmur is heard over the sternum and occasionally over both lungs. Ordinarily they cause no circulatory disturbances.

Combined Valvular Lesions.—The effects of valvular disease may be best studied when there is a simple stenosis or insufficiency of a single valve, and when no complications are present. Yet such simple cases are rare. In the right heart we frequently find associated defects in development; in the left heart, combinations of several valvular lesions. Pure mitral insufficiency is comparatively frequent, but uncomplicated cases of mitral stenosis, or of aortic insufficiency or of aortic stenosis, are much rarer than are the combinations of mitral insufficiency with mitral stenosis, aortic insuffiency with aortic stenosis or aortic insufficiency with double mitral disease. The aortic semilunar valves are closely adjacent to the aortic segment of the mitral valve, and when the latter is diseased the former are also frequently affected.

The effect of a combination of valvular lesions is the resultant of the effects of the individual lesions. They may even tend to neutralize each other so that the combination is less harmful than are the individual lesions. For example, the dilatation of the left ventricle resulting from aortic insufficiency may be lessened by an associated aortic stenosis; and although both mitral insufficiency and mitral stenosis act similarly in damming the blood back into the lungs, they tend to neutralize each other so far as their effect upon the left ventricle is concerned. Indeed, we may say in general that the stenosis which so often follows a valvular insufficiency may be of advantage in that it limits the amount of blood which regurgitates. Caution is indicated, however, in deciding this question in the individual case, for other factors, especially the condition of the heart-muscle, are often of paramount importance.

Hypertrophy of the Right Ventricle.—The work of the right ventricle is directly dependent upon the condition of the pulmonary circulation. Anything that increases the pressure in the pulmonary vessels increases the resistance against which the right ventricle must force the blood. We have seen an illustration of this in the case of mitral valve disease. Similar effects may result from a weakened left ventricle which cannot com-

pletely empty itself during systole. Its power of suction in early diastole is also diminished, for this power depends upon the elastic rebound after a powerful contraction,[37] or possibly upon an active process in the muscle-fibres themselves.[38] The unexpelled blood in the ventricle and the lessened suction hinder the entrance of blood from the lungs, raise the pressure in the pulmonary circulation, and so increase the work of the right ventricle. We have seen that the left ventricle can alter its elasticity under certain circumstances, enabling it to hold a larger amount of blood in each diastole, and the question naturally arises, "Why does not the weakened ventricle do this instead of damming the blood back into the lungs?" The reason seems to be that the muscle tissue is so diseased that its elasticity as well as its contractility is diminished.

Primary disturbances of the circulation in the lungs may likewise affect the right heart. We know that the resistance to the blood-flow in the pulmonary vessels is normally very slight. Though large vascular areas, even up to three-quarters of the total, may be thrown out of function, a sufficient amount of blood may still be sent through to the left ventricle.[39] The right heart simply propels the blood through the remaining pulmonary vessels with a greater velocity. The open vessels are, indeed, dilated, but not sufficiently to compensate for the others thrown out of function, so that the pressure in the pulmonary artery rises. The dilatation of the vessels remaining open is quite different from that which takes place under corresponding circumstances in the greater circulation. In the latter, when a vessel is closed, the general pressure does not necessarily rise, because vasomotor influences may produce a compensatory vascular dilatation in other parts of the body; in the lungs, the resulting dilatation is purely passive, and is due to the increase of pressure in the pulmonary artery caused by the obstruction in one of its branches. This increased pressure necessitates an increase in the amount of work done by the right ventricle, which will be greater or less in any given case, depending upon the number and dilatability of the pulmonary vessels remaining open. In case the increased work persists for some time, hypertrophy of the right ventricle will ensue.

For this reason the right ventricle becomes hypertrophied as a result of sclerosis of the pulmonary artery (a rare

condition); also in those more frequent pulmonary diseases which lead to destruction or compression of the vessels, such as cirrhosis of the lungs from various causes, chronic pneumonia, pulmonary emphysema and thoracic deformities.[40] Long-continued bronchitis is often described as a cause of hypertrophy of the right ventricle, and especially as a cause of the enlarged right heart found in children who are subjects of this disease. It is difficult to say whether the bronchial inflammation directly increases blood pressure or whether the continual coughing gives rise to the hypertrophy of the right ventricle by its effect on the intrathoracic pressure.

It has often been asserted that we have in tuberculosis an exception to the general rule that chronic pulmonary disease leads to hypertrophy of the right ventricle. To account for this supposed exception, numerous explanations have been offered, one of which is to the effect that the total quantity of blood is diminished in this disease. We now know, however, that tuberculosis is no exception to the general rule. Anatomical investigations[41] have shown that, in proportion to the body weight, the weight of the right ventricle is increased in a large proportion of those who die of consumption. Clinical evidence supports the same view, for it is not uncommon to find an accentuation of the pulmonic second sound in tuberculous patients. Nor from the orthodiagraphic method[42] can any other conclusion be drawn. To what extent individuals of the tuberculous habitus are endowed with especially small hearts, and what bearing the latter have on the development of the disease, are questions that cannot be entered into in this place.[43]

Extensive pleuritic adhesions may also lead to an hypertrophy of the right ventricle. Their interference with the movements of the lungs doubtless deprives the pulmonary circulation of the assistance in the aspiration of the blood usually derived from these movements, so that additional work is thrown on the right ventricle.

Hypertrophy of the Left Ventricle.—The work of the left ventricle is made greater by any increase in the resistance to the flow of blood through the peripheral arteries. A temporary increase in resistance arising from vasomotor influences is not an uncommon physiological occurrence.

Of considerable importance as a cause of permanent increase in the arterial pressure are certain forms of arteriosclerosis.[44] When the elasticity of the arteries is diminished, they offer a greater resistance to dilating forces; but once having been dilated they do not so easily recover their original size. Various opposing factors must, therefore, be considered. The rigidity of certain areas may be neutralized by dilatation of other areas. There is also a tendency for the affected vessels to become permanently dilated. The precise effect of these various opposing factors can only be determined by experimental investigations.

As a matter of fact, hypertrophy of the left ventricle develops in only a small proportion of patients with uncomplicated arteriosclerosis. Those types accompanied by hypertension are the ones which regularly exhibit such an hypertrophy. It is present, therefore, especially in cases of sclerosis of the first part of the aorta and in extensive sclerosis of the splanchnic vessels. The splanchnic arteries are of such paramount importance in controlling the peripheral resistance that when they are diseased it is difficult or impossible to attain compensation by a dilatation of other vascular areas. Other uncomplicated cases of arteriosclerosis rarely show any marked degree of heart hypertrophy. The frequency of hypertension in arteriosclerosis is still undetermined. Besides the paramount influence of the localization of the process, as noted above, there are other factors, such as the social status, mode of living and perhaps race, that play a rôle.[45] Hypertension is distinctly more common in the well-to-do.

Various complications often render it extremely difficult to estimate the effect of arteriosclerosis upon the heart. The same cause that induces the disease of the arterial walls may also independently act upon the heart muscle. As examples of such causes, we may name the excessive use of alcoholic drinks, of coffee and of tobacco, severe and continued exertion, infectious diseases, and, above all, syphilis. Then, too, arteriosclerosis itself may lead to degeneration of the heart muscle owing to an involvement of the coronary arteries. Finally, an associated chronic nephritis may produce an hypertrophy of the heart. We thus see how extremely difficult it is,

in the individual case, to determine whether the arteriosclerosis is the direct cause of the heart hypertrophy or whether the latter is due to some associated condition.

Another important question revolves about the point as to whether arteriosclerotic hypertension is due to the anatomical changes in the vessel-walls, or to an augmented vascular tonus, as is the case in the nephritides. (Indicative of the latter hypothesis is the reported therapeutic efficacy, in some cases, of papaverin, the action of which, as pointed out by Pal,[46] is to cause a relaxation of smooth muscle. Excellent results have been recorded in cases of uræmia due to vascular spasm, *e.g.*, in scarlatinal nephritis, as contrasted with the type founded on extensive anatomical changes in the renal vessels.—Ed.) In any event, the determining moment will reside in the involvement of the root of the aorta, or of a large number of smaller vessels. Angina pectoris and intermittent claudication are classical examples of conditions in which vessel spasm plays an important part. (And papaverin has likewise been found of great value in the former. Experimentally, the drug causes a dilatation of the coronary arteries.[47]—Ed.)

The left-sided hypertrophy accompanying aneurism of the aorta[48] is to be ascribed to some complicating condition. It is difficult to see how a dilatation of the vessel would increase the work of the heart, and, as a matter of fact, we do see patients with aneurisms in whom there is no enlargement of the left ventricle. When the latter occurs, we can usually ascribe it to the arteriosclerosis—generally luetic—present, or to an associated aortic insufficiency. Interesting in this connection are the observations[49] indicating that hypertrophy of the left ventricle and an increase in the elastic elements in the aorta may follow the inhibition of regulating influences via the depressor nerves.

Hypertrophy of the left ventricle may result from that rare condition, congenital stenosis of the aorta.[50] Such a narrowing would increase the work of the heart by offering a greater resistance to the blood-flow. In this anomaly, the hypertrophy may not develop until late in life. If such be the case, we may assume that the stenosis produced but little effect so long as there were no great demands upon the heart, but that the hindrance made

itself felt when a more active circulation was rendered necessary by the exertions of later life.

Severe dyspnœa causes a marked rise in blood-pressure, and it has long been a question whether moderate dyspnœa continued over a long period of time may not give rise to hypertrophy of the left ventricle. From recent observations,[51] we know that persons with chronic dyspnœa do show an unusually high arterial pressure, and there is reason to believe that this may ultimately produce an hypertrophy of the left ventricle.

Hypertrophy of Both Ventricles.—Hypertrophy of both ventricles is produced by causes that increase the work of both. Pericardial adhesions with mediastinitis are usually reckoned among such causes; and it is easily conceivable that these conditions might throw extra work upon the heart, which must now move surrounding structures, even the chest wall, with each contraction. As a matter of fact, we frequently find heart hypertrophy associated with chronic pericarditis. It is questionable, however, whether any causal relation exists between the two, for in some cases no hypertrophy is present, and, indeed, the heart may be atrophied. Since pericarditis is often associated with disease of the heart muscle, the cases that show hypertrophy should be studied with especial regard to the effect which these myocardial changes may have had in the production of the hypertrophy.

It is theoretically possible that an increase in the number of beats per minute might lead to hypertrophy of the heart. Such an increased heart-rate is seen in nervous people, especially in association with hyperthyroidism or sexual excesses. In our opinion, a more powerful heart-beat, sensed by the patient as a palpitation, is another important cause of heart hypertrophy, even in the absence of an accelerated beat. It has been shown, furthermore, that in hyperthyroidism the blood-pressure is frequently above the normal, due apparently to an excitation of the vasomotor system.[52] The conditions necessary to produce an hypertrophy are, therefore, present, and as a matter of fact, it is not uncommon to find enlargement of the heart accompanying thyreotoxic states. It is probable, nevertheless, that this hypertrophy is due not so much to the rapid and forcible heart-beat as to the direct action of toxic substances.

Tobacco, especially in the form of heavy cigars and when burned in short-stemmed pipes, is also said to cause heart hypertrophy. The action is, undoubtedly, toxic in nature.

Cardiac Changes in Renal Disease.—The influence of renal changes upon the heart presents a problem of considerable difficulty.[53] In the majority of cases of acute and chronic Bright's disease, there is an increased blood-pressure which, if of more than four weeks' duration, leads to hypertrophy of the heart. The left ventricle is first affected, and though anatomical studies would indicate that there is a frequent coördinate involvement of both the left and right ventricles, it is clear from the studies of Hirsch[54] that the former is the primary. Indeed, as Pässler[55] has shown, the right heart hypertrophies only after the left has become insufficient, the conditions being in nowise different, therefore, from those obtaining in valvular disease of the left heart.

Accordingly, the increased demands made upon the left ventricle must be the starting point of all inquiries into the origin of nephritic heart hypertrophy. Thus, we have a clear-cut and valuable analogy in the hypertrophy incident to arteriosclerosis. The first point to be determined is whether the type of the nephritis present governs the development of increased arterial pressure and of hypertrophy. The latter are, in my opinion, regularly absent in those nephritides due to toxic disturbance of the epithelial cells, as in arsenic, mercury and phosphorus poisoning, and also in the group following the acute infections (diphtheria, typhoid fever, sepsis). In scarlatinal nephritis, hypertrophy is of variable occurrence; and in the so-called acute primary form, it is also occasionally observed. These primary types, incidentally, will be diagnosed less frequently as we become better equipped to recognize that they are often secondary to latent infections.

Among the chronic nephritides, the contracted kidney is most often associated with heart enlargement; in this form, indeed, the hypertrophy attains its highest grade. Yet there are typical examples of granular atrophy of the kidney in which both the arterial tension and the size of the heart are normal.[56] In the so-called chronic interstitial and chronic parenchymatous types, hypertension is also frequent, though in the latter it is often absent—indeed, in the majority of

cases according to some observers.[57] Pure amyloid kidney leads to no heart changes. Conditions such as renal stone and tumors of the lower abdomen, causing pressure upon both ureters and leading to chronic hydronephrosis may also be followed by hypertrophy according to Cohnheim; yet this is surely an infrequent event. (Chronic infections of the renal pelves, even though entailing no obstruction to the flow of urine, not infrequently lead to changes in the size of the left ventricle and in the arterial tension as pronounced as those seen in granular kidneys; and they may likewise terminate in uræmia. The differential diagnosis in such cases may be exceedingly difficult.—Ed.)

It is evident, therefore, that *there is no constant relation between the type of nephritis and the occurrence of hypertrophy*, though an enlargement of the heart is most frequent and most pronounced in cases of genuine contracted kidney. Nor is there a definite relationship existing between the localization of the renal process and the appearance of circulatory changes, for the particular tendency of glomerulonephritis in this direction has not been proved.[58] Indeed, I am almost inclined to agree with those who believe that nephritis, as an anatomical process, has no effect upon the heart and blood-pressure, and that the latter suffer changes only as a result of functional disturbances initiated by the nephritis.

The theory that the rise of blood-pressure is due to an augmented viscosity of the blood[59] *is scarcely tenable*, for though the work of the heart would thereby be increased, the blood-pressure would be kept at its normal level by a compensatory regulation of vascular tone. And, furthermore, observations indicate that the viscosity of nephritic blood does not differ from that of the normal.

A general decrease in the calibre of the blood-vessels would explain everything, for even a slight diminution, either in all the vessels or in the more important vascular areas, would greatly increase the work of the heart, since this varies inversely as the fourth power of the diameter of the combined vessels. Such a change in diameter, if present, must take place within a short space of time, as in acute nephritis, and must last for years, as occurs in chronic interstitial nephritis. A permanent narrowing of this sort might be due to disease of the smaller arteries, itself either secondary to the nephritis or co-

ordinate with it. The latter conception is the more reasonable, because it is scarcely likely that the noxious element leading to heart hypertrophy in renal disease confines its action to the kidneys alone. This subject will be considered again under nephritic œdema (p. 92).

That the cardiac hypertrophy and the hypertension observed in nephritis are due to changes in the peripheral blood-vessels is a classic conception and one based on considerable evidence.[60] Thus, well-defined arteriosclerosis is frequently associated with contracted kidney; further, the arteriocapillary fibrosis of Gull and Sutton occurs in granular kidney; and in a number of nephritides, acute inflammatory changes in the vessels have been noted. Jores, in a comprehensive and careful study, noted the frequency and extensiveness of changes in the small vessels both of the kidneys and of other organs. These changes may augment the work of the heart, and raise the arterial tension in a purely mechanical way by increasing the peripheral resistance; but, in addition, the origin and persistence of the high tension point with great probability to an altered functional condition of the vessels.[61] That vascular disease leads to an irritable vasomotor condition has already been noted in connection with atheromatous heart hypertrophy (p. 22).

On the other hand, the origin and nature of the increased arterial pressure in renal disease point with certainty to an altered functional condition of the vessels. The hypertension develops early in acute nephritis, and during the course of acute and chronic nephritides, the blood-pressure is subject to sudden and excessive variations. It readily rises as a result of excitement, exertion, abundant mixed food, and, most of all, as a result of impending uræmia. It is lowered by a quiet life and a careful diet, *e.g.*, milk. In all renal diseases associated with high blood-pressure, we frequently encounter considerable variations of pressure for which no cause is apparent.

It seems to me that these facts can only be explained by assuming a contracted state of the smaller arteries which is liable to sudden and excessive variations. One might naturally object to

the assumption of a continued arterial spasm which lasts for years. This is not what is here assumed, however. It is well known that the arteries are normally maintained in a condition of partial contraction and that this so-called tonus is largely regulated through the nervous system, perhaps through an intermediate and continuous epinephrin action (see p. 336). It seems to me most probable that this normal tonus is increased in nephritis, and that this causes the cardiovascular symptoms of this disease.

Thus we may say that in association with nephritis there arise conditions favoring an increase in vasomotor tone. It is not unlikely that it is brought about by a pressor action exerted by the toxic materials that are retained. Possibly on this basis is to be explained the beneficial effect in high tension cases of a milk diet, in that it throws no added strain upon the already overburdened kidneys, thus enabling them to excrete the uræmic toxins. Our ignorance of the nature of these poisonous end-products is no proof that chemical processes are not at work in the production of high tension. Indeed, we are not as yet entirely informed as to the substances which are excreted by the glomeruli.

French observers have called attention to the possibility of the coexistence of nephritis and disease of the suprarenal glands, or other portions of the chromaffin system. In the light of our present knowledge of the hypertensive action of epinephrin, there is no theoretical objection to this hypothesis; on the other hand, the epinephrin content of the blood has not been found increased in nephritis.[62] As to the interesting observation that the kidney tissues themselves contain substances which raise the arterial pressure, little can at present be said.[63] In an examination of diseased kidneys, for instance, the amount of such pressor substances was found not abnormally large; nor is the presence of pressor bodies peculiar to the kidneys.

The foregoing discussion of the etiology of the cardiovascular changes in nephritis leads naturally to a consideration of their possible significance. The increase in the normal vascular tonus is apparently of benefit in the secretion of urine, for the filtration processes in the glomeruli demand a certain capillary pressure and a certain capillary flow. If the glomerular surface be diminished, then less blood would come in contact with the glomerular epithelium and

less urine would be secreted. An increased arterial pressure with an increased glomerular flow will cause an increased secretion from the healthy glomeruli and possibly from the diseased ones as well. The increased arterial pressure then becomes advantageous to the kidneys. At the same time, as we shall see (p. 34), it may be a source of danger to other parts of the body.

We may sum up what we have said concerning the factors concerned in the causation of nephritic hypertrophy of the left ventricle by regarding the matter from a different, and, in my opinion, better-founded point of view. Mention has been made of the fact that nephritis as such need have no effect upon the circulation; that the majority of nephroses are unaccompanied by circulatory changes; and that in nephritides associated with hypertension, arterial changes are always present. On the other hand, we meet with cases showing similar arterial changes, accompanied by an increased blood-pressure and by an enlargement of the heart, clinically indistinguishable from that occurring in granular atrophy of the kidney, but in which the kidneys are quite normal; or, if definitely diseased, the type of the affection is obscure (see under Hypertension, p. 84). I am more and more convinced that these cases, which unquestionably are more frequent than is the genuine contracted kidney, cannot fundamentally be distinguished from the latter; and in this view I am upheld by many.[64] It is an error, in my opinion, to emphasize the renal changes present in such cases. On the strength of the investigation of Jores, we are justified, I believe, in attributing the heart hypertrophy and arterial hypertension of most, if not all, cases of nephritis, of arteriosclerosis, of the so-called essential hypertension and of syphilitic hypertension, to the concomitant action of vessel-wall disease and functional vascular disturbances. This, however, does not solve the genetic relation between the arterial and renal changes. I believe that we have to do with a more or less generalized process affecting the kidneys and vessels, equally and simultaneously.

The "Athlete's Heart."—As has been previously stated, severe muscular exertion ordinarily increases the weight of the heart in the same ratio as it increases the weight of the general musculature. It is frequently assumed, however, that hyper-

trophy of the heart may result from prolonged muscular exertion. Such a relative increase in the heart's weight does perhaps occur in individual cases in the absence of any impairment of function, but this is certainly exceptional (see p. 8). When over-activity affects the heart, it usually does so by causing a primary weakness of the muscle; yet here again it may frequently be questioned whether this weakening should not be attributed to some other associated causal agent, such as the excessive use of alcoholic liquors, arteriosclerosis or renal disease. Further observations upon these questions are, therefore, necessary.

The recent orthodiagraphic observations[65] relative to a diminution in the size of the heart following severe muscular exertion are subject to two possible interpretations, *viz.*, that a functionally efficient organ empties itself more completely in systole than under normal conditions, or that the rapid heart action does not allow a proper diastolic filling of the chambers and that the reduced orthodiagraphic figure, therefore, is an evidence of beginning myocardial insufficiency.

The "Beer-Heart."—It is not uncommon to find weak hearts with an hypertrophy of the muscle and a dilatation of the cavities in men who have been accustomed to drinking very large quantities of beer. Such hearts are most frequently seen in Munich, and may show extreme grades of hypertrophy. Excessive wine-drinkers ocasionally suffer from a similar condition, whereas drinkers of more concentrated alcoholic liquors are only very rarely affected in this way; they tend to develop cardiac weakness unassociated with hypertrophy. In many beer-drinkers no other etiological factor is present except the immoderate use of beer. The majority, however, do very heavy work, and consume large quantities of food in addition to their beer.

That the kidneys, or at least the blood-vessels, are concerned in this type of hypertrophy seems likely from the observation of F. Müller[66] that the majority of beer-drinkers exhibit a more or less marked increase in blood-pressure. The entire question, therefore, must be elaborated again. Perhaps the conditions here are similar to those underlying cyanotic induration of the kidney.

The cause of the enlargement of the heart in beer-drinkers has been ascribed by some to an increase in the total amount of

blood, a genuine plethora. Autopsy studies apparently give substance to this hypothesis. Experiments have been made to show the effect of such a plethora upon the heart.[67] In rabbits in which a genuine polycythaemic plethora was produced and maintained for several months by injections of an homologous blood, the weight of the heart was found not increased. Accordingly, the work of the heart could not have been augmented. For our purpose, these experiments lack the accessory factor residing in the alcohol.

Personally, I have observed these heart changes in brewers, laborers and students who drank immoderately, and who also did heavy work, or took violent exercise. A number of such people certainly did not give the impression of being "full-blooded." It seems to me that the combination of beer-drinking with heavy work was responsible for the heart condition; and indeed I gained the impression that both the dilatation and the hypertrophy tended to disappear if the patient changed his manner of living.

Gourmands may at times acquire a similar heart condition, probably from the large amounts of food and wine, the heavy smoking and the not infrequent sexual excesses. In such cases the picture is often complicated by arteriosclerosis and nephritis, and myocardial weakness is generally prominent. Incidentally, we may observe that the injurious action of tobacco upon the vessels is now a well-recognized fact.

The Heart in Pregnancy.—It has been frequently asserted, especially by French observers, that there is an enlargement of the heart during pregnancy. As a matter of fact, in pregnancy, as in other conditions associated with a high position of the diaphragm, the area of cardiac dulness is enlarged because the heart approaches the chest wall. The truth is that pregnancy exercises no effect on the heart other than that which could be explained by the general increase in the weight of the body.[68]

The Ability of the Heart to Hypertrophy.—It may be asked, What conditions influence the power of the heart to hypertrophy? We may mention three factors. In the first place, there is the rapidity with which the new demands are made on the heart. If, as usually occurs, the work is gradually increased, the heart has time to hypertrophy gradually and to attain ultimately an enormous size and greatly increased

working capacity. In the second place, the degree of hypertrophy is influenced by the amount of new work required. The more work the heart does, the greater is the resulting hypertrophy. As has been said, an enormous increase in work may be accomplished, provided the new demands are gradually increased. Yet even sudden calls upon the healthy heart are well responded to up to a certain limit. We can give no definite figures for this limit in man, but we know from clinical experience that it is not a low one. Experimentally, it has been shown that the heart of a healthy dog is able to pump six times the customary quantity of blood, and to overcome three times the usual blood-pressure.

The third and most important factor that influences the heart's capacity to hypertrophy is the condition of the cardiac muscle. Without a healthy muscle, the heart cannot accommodate itself to an increase in work. The general nutrition of the body is of comparatively little significance, for Tangl[69] has shown that even in the most emaciated animals hypertrophy of the left ventricle will develop after an artificial valvular lesion. We have no right, therefore, to attribute a lack of hypertrophy to the poor general nutrition of the patient. It is to be attributed solely to the fact that there has been no increase in the work of the heart, which, in our opinion, is the case in amyloid kidney. When additional work is required of the heart, there are only two possibilities—either it responds and hypertrophies, or it weakens. It is, of course, probable that when the body is well nourished the heart is better able to respond and is less likely to weaken. We may mention here that in childhood the heart possesses far greater powers of adaptation than in later life, and that it is then able to compensate to a very marked degree.

Concentric and Eccentric Hypertrophy.—The heart hypertrophies discussed thus far may be divided into two general classes, according to the size of the ventricular cavities. When the muscle increases with no enlargement of the cavity, we speak of a simple (concentric) hypertrophy. On the contrary, the size of the cavity may also increase, and such a condition is called an eccentric hypertrophy. This division is applicable only to hearts which are properly compensated. As soon as this fails, dilatation of a totally different nature occurs, which shall be discussed later.

The ventricular cavity must become dilated during diastole

whenever it is necessary to pump more blood at each beat. Whether the cavity is also dilated in systole, or not, depends upon the completeness with which the ventricle empties itself. Experimental evidence would lead us to the belief that an incomplete expulsion of the blood is by no means infrequent. In heart-failure this is the rule; but even when the heart is maintaining a good circulation it does not empty itself completely when very large amounts of blood must be propelled, or when the resistance is much increased. Yet hypertrophy may occur even in a ventricle which does not empty itself completely, so long as the work of the heart is increased and the myocardium is responsive.

The Inefficiencies of a Compensated Circulation.—The hypertrophy which enables the heart to carry on the circulation under pathological conditions is spoken of as a compensatory hypertrophy. This does not mean that the new circulatory mechanism is just as effective as the old. According to the view of Romberg and of the author, however, the power of the hypertrophied heart muscle to accommodate itself to further new demands is equal to that of the intact muscle.

Martius and Aschoff,[70] on the contrary, regard the reserve power of such a heart as inferior to that of the normal organ, and explain thus the ease with which the owners become fatigued. Yet we know that it is not uncommon for individuals with hypertrophied hearts to perform as much physical work as the healthy. And, as Romberg has shown, animals with aortic insufficiency are able to meet demands upon their heart muscle in a way that would indicate that the myocardial reserve force is equally as great as that of a non-hypertrophied organ.[71]

Hypertrophy, therefore, may be regarded as of great advantage to the heart in these cases, for it not only enables the latter to accommodate itself to additional burdens, but also, within certain limits, makes possible the maintenance of the circulation at practically the same efficient level as in health.

In the foregoing discussion we have taken the ground that hypertrophy in all cases represents the response of the cardiac muscle to increased work. The views of earlier writers differed from this; thus Buhl ascribed the hypertrophy in nephritis to inflammatory changes in the myocardium. And even Albrecht[72]

regards hypertrophy as the first stage of a progressive myocarditis, and to the latter and the accompanying degenerative changes he ascribes the eventual weakening of the heart. I am free to admit that this conception of an inflammatory hyperplasia offers an attractive solution of certain types of hypertrophy not explainable on a mechanical basis. The proof that this is the case, however, is lacking.

And yet, as has been stated, a compensatory enlargement of the heart cannot restore the circulation to a normal condition, and for many reasons. In the first place, the blood-pressure in the pulmonary system must frequently be maintained at a higher level than usual, as happens in many diseases of the left heart and of the lungs (see p. 19). If the high pressure in the pulmonary circulation continues for any length of time, the connective tissue of the lungs increases and small quantities of blood are extravasated. The resulting pigment is taken up by the alveolar epithelial cells, and if these appear in the sputum, they are diagnostic of chronic passive hyperæmia of the lungs (heart-failure cells). The increased pressure in the pulmonary system, if at all marked, unquestionably interferes with breathing.[73] The tissues of a lung that is the seat of chronic passive hyperæmia also seem to suffer in their nutrition and in their resistance to infection. At least, such patients are very susceptible to bronchitis, so that it seems as if the lungs had become less able to resist organisms that may have entered through the upper air-passages. And, in addition, atypical pneumonias are not infrequently seen.[74]

Lesions of the right side of the heart not infrequently lead to stasis in the veins of the general circulation. Since the same condition is produced by any weakness of the right ventricle, it will be considered in that connection.

All patients with continuously high arterial pressure are in danger of the rupture of an artery, which is especially true if the walls of the arteries are already weakened. The immediate cause of the hemorrhage is usually some act which itself produces a further rise in pressure, such as excitement, violent exertion, coitus and straining at stool. In patients with arteriosclerosis or granular kidney, such acts are not infrequently followed by hemorrhages into the brain or retina.

As is well known, the characteristic pulse of aortic insufficiency is one of great excursion. It bounds up against the palpating finger, and as suddenly recedes. It may be transmitted to the capillaries, producing a visible capillary pulse. Such a pulse is not without its effect upon the arterial wall. The rapid and excessive distention may result ultimately in a stretching of the artery, so that vasomotor influences are no longer able to reduce it to its former size. The amount of blood in the body is limited, and, since the dilated arteries contain more than normally, there may thus result an inadequate filling of the rest of the vascular system.[75] This is perhaps the explanation of the poor circulation sometimes seen in cases of aortic insufficiency in which there is no weakening of the left ventricle.

Still another effect of an enlarged heart must be mentioned, *viz.*, the space taken up in the chest cavity and the resultant compression of the other intrathoracic organs.

The foregoing considerations relative to hypertrophied hearts are applicable to the individual case in variable degree, depending upon what part of the heart has undergone hypertrophy, and upon the cause of the latter. Certain valvular lesions, therefore, are less unfavorable than others; thus an aortic insufficiency of moderate grade or a combined aortic lesion tend to be less injurious in their effects than do certain mitral affections, in that the former involve the pulmonary circulation to a lesser degree.

We have dealt thus far with the heart's condition so long as the body is at rest. If patients with heart disease exercise, the work of the heart is at times enormously increased. Thus we see that although the hypertrophy of the heart may compensate for the valvular lesion in certain particulars, it cannot restore the circulatory conditions to their normal state.

Myocardial Changes in Hypertrophied Hearts.—And yet the chief source of difficulty with an hypertrophied heart does not lie in any of the factors thus far mentioned, but rather in the condition of the muscle itself. We have enlarged upon the fact that a healthy hypertrophied muscle possesses capabilities not differing from those of the normal muscle. The hypertrophied heart muscle and the enlarged biceps of the athlete are comparable in some cases, but, unfortunately, it is not so in the

majority of instances. For the very causes which lead to hypertrophy of the heart often, at the same time, produce pathological changes in the myocardium. It will be recalled how frequently the infectious diseases give rise to valvular lesions and consequently to heart hypertrophy. In such infections the myocardium is almost invariably diseased, and often to a greater degree than the endocardium. These diseases, and especially acute articular rheumatism, cause degenerations of the muscle fibres, interstitial myocardial inflammations and diseases of the arteries. It is indisputable that these disturb the functions of the heart muscle most seriously.[76] Such a disturbance may take the form of an acute dilatation—which is not of a compensatory nature, due to the necessity for an increased supply of blood—but which results from the incomplete contractions of the heart-muscle. The dilatation of the right ventricle in the early stages of a mitral lesion is usually of this nature. Chronic myocardial changes are likewise of great importance in the subsequent course of a valvular disease.

Though observers are not agreed as to the frequency of well-marked myocardial changes in valvular affairs—Aschoff, for example, believing that the significance of such changes is greatly overestimated[77]—yet clinical experience has shown that the efficiency of the heart-muscle plays a very important part in the maintenance of the circulatory equilibrium. But as our present knowledge of the anatomical alterations in the myocardium is insufficient to explain its functional disturbances, there has sprung up, very naturally, considerable speculation relative to muscular injuries which have escaped our notice. Looking at the problem in the broadest way, we can say that even the infectious myocardial lesions are evidence simply of the action of some harmful chemical influence. And as the extent of a myocardial process cannot be taken as the measure of the diminished capabilities of the heart, I must admit that some cases of insufficiency are insusceptible of explanation on the basis of the anatomical changes present.

We may sum up then as follows: The insufficiencies of many valvular hypertrophies are due to a damaged heart muscle, itself in certain cases the result of inflammatory processes. The

latter may vary both in location and intensity, and bear no definite relation to the kind or age of the valvular lesion. It adds an uncertainty to the prognosis of valvular disease which must always be taken into account. The progressive character of the processes in question is another source of uncertainty. On the one hand, the endocarditis may gradually progress and lead to more and more extensive alterations in the valves; while, on the other hand, the heart muscle may gradually weaken so that it becomes less and less able to respond to the increased calls made upon it. A most unhappy combination!

The weakness of the hypertrophied heart muscle in valvular conditions, apparently not of infectious origin, is less easily explained. Hypertrophy of the right ventricle often arises from diseases of the lungs. The progressive character of the pulmonary disease may gradually throw an overwhelming burden upon the right ventricle. In other cases, however, no such explanation is possible, and we are entirely ignorant of the reason why the hypertrophied ventricle weakens.

So far as the left ventricle is concerned, the relations are comparatively simple when the hypertrophy is consequent to arteriosclerosis, for it is well known that the coronary arteries are frequently involved in this process and that coronary sclerosis leads to most serious disturbances in the nutrition of the heart muscle.

The hypertrophied hearts of patients with nephritis are often singularly free from signs of weakness. Many patients with granular kidneys maintain a good circulation for years, and only in the last stages of the disease do they develop signs of cardiac weakness and of uræmia. Albrecht[78] has recently shown that in such cases disease of the myocardium, sufficient to account for all symptoms, is present.

It is extremely difficult to explain the cardiac weakness that develops as a result of the abuse of beer and wine, and also of excessive physical exertion. In a number of these cases, the extensive fatty degeneration and the fresh inflammatory processes are sufficient to account for all the symptoms; but no satisfactory explanation can be given of those cases in which there is cardiac weakness without

demonstrable signs of disease in the myocardium. Further studies are necessary to throw light on such conditions.

We can now understand how it is that in many instances the hypertrophied heart is less efficient than the normal organ. Hypertrophy itself does not necessarily entail any weakness. Theoretically, the hypertrophied organ possesses the same reserve force as the healthy one. Such favorable hypertrophies are, indeed, observed, but unfortunately they are rare. In the majority of cases the cause which induces the hypertrophy also damages the capabilities of the muscle. The heart is so injured that it cannot properly respond to an emergency at the very time when its power to do so is most needed.

For this reason, many hypertrophied hearts are unable to meet any additional call made upon them. They tire much more readily than the normal organ, and when once tired they do not recover so quickly; indeed, a serious or even irreparable damage may result. On this account, the patient with heart disease is repeatedly warned of the dangers of over-exertion. On this account, also, women who have heart disease often do badly during a confinement.

Causes of Broken Compensation in Hypertrophied Hearts.—If a heart becomes unable to meet the increased demands that are made upon it, we speak of a break in compensation. This failure in compensation may be brought about in several ways. In the first place, *what is ordinarily a moderate call upon the heart may be an excessive one in certain forms of disease.* Or, it is conceivable that *inflammatory processes* at work in the heart muscle interfere with, or even render impossible, its recovery; for in a functionally impaired tissue, morbid processes find a good soil for extension.

It frequently happens that a break in compensation occurs even though the patient has taken great care not to exert himself. Such a break in compensation may improve, and even be recovered from; but, on the other hand, it may lead to permanent insufficiency or death. The prognosis is decidedly better when the compensation of the right ventricle is alone at fault; and the breaks in compensation which occur in mitral disease are decidedly more favorable than those which develop in a heart in which the

left or both ventricles are hypertrophied as a result of continued, severe exertion, arteriosclerosis or active valve disease.

In a certain proportion of the cases in which such a decompensation occurs, apparently spontaneously, it is to be attributed to a fresh infectious process involving the heart muscle. A second attack of acute articular rheumatism, a pneumonia or a tonsillitis may in this manner be the immediate cause. It seems as if the hypertrophied heart muscle formed a *locus minoris resistentiæ* to the infecting organisms or to their toxins.

In another group of cases the apparently spontaneous break in compensation is due to the progressive character of the process that caused the hypertrophy. The demands upon the heart are gradually increased to such an extent that they cannot be carried out. Among such progressive processes are to be reckoned many valvular lesions, pulmonary cirrhosis and emphysema, arteriosclerosis, chronic nephritis and the excessive use of beer; in a word, they include the majority of all the causes of heart hypertrophy.

Finally, the break may occur, not from any increase in the demands upon the hypertrophied heart, but from a progressive weakening of the muscle through myocardial disease, which renders the heart unable to do even its normal quota of work. This form of cardiac weakness will be more fully considered below.

In a certain, though relatively small, number of the cases, therefore, we are familiar with the causes of transitory and permanent disturbances in compensation. In particular, we are ignorant as to the factors concerned in the majority of those more or less rapid decompensations occurring in hypertrophied hearts and which recover upon the proper administration of digitalis (see also Auricular Fibrillation, p. 65).

The active principles of this drug stimulate both the myocardium and the cardiac vessels to more efficient contractions.[79] To be efficacious, therefore, digitalis must encounter a myocardium which is still responsive. Herein lies the great prognostic value of the preparation. Though of little apparent service in the fresh inflammatory cardiac lesions, it is eminently successful in many of the classical decompensations. Whether the action of digitalis is physical, counteracting abnormal swelling of the

muscle fibres, or chemical, restoring an altered sodium chlorid balance, are questions requiring further elaboration.

It is a noteworthy fact that in the stage of broken compensation the arterial blood-pressure is often, and according to some observers, always increased[80] (Hochdruckstauung, Sahli). To explain this we must fall back upon Traube's hypothesis, *viz.*, that vasomotor irritability is responsible (see also p. 85).

Causes of Primary Insufficiency of the Heart Muscle.—Some of the causes that lead to a primary weakness of the heart muscle have already been mentioned in the last section. The others may affect either hypertrophied or non-hypertrophied hearts.[81]

Of first importance among such causes are those which interfere with the blood-supply to the cardiac muscle, such as thrombosis, embolism and sclerosis of the coronary arteries. The heart is exceedingly sensitive to changes in its blood-supply.[82] Though the heart of a healthy rabbit has been shown capable of withstanding an interrupted blood-supply for a period of six minutes,[83] yet any prolonged ischæmia is as badly borne by the heart as by any other organ. Hence the importance of Eppinger's[84] observation that the vessel diameter in hypertrophic and insufficient hearts is diminished. If a large portion of its wall be suddenly deprived of its nourishment, the organ stops beating. This has been observed clinically when an embolus has lodged in a coronary artery, and it has been demonstrated experimentally by ligating one of the circumflex vessels. In other cases, where the damage is less extensive, the muscle wall may degenerate and rupture, leading to a fatal hemorrhage within the pericardial sac.

The effect of occlusion of a smaller branch of a coronary artery is variable. The usual consequence is a weakening of the affected ventricle, a fall in pressure in the efferent arterial trunks, and a rise in venous pressure. In some instances the patient experiences a sensation of oppression or of severe pain in the precordium, which may or may not herald a fatal termination. Arrhythmia is usually present, and the rate is at first slow and later accelerated. The heart may stop in fibrillary twitchings, a condition in which the different muscle fibres contract incoördinately and therefore uselessly. Porter[85] has

shown that it is possible to tie even large coronary branches without causing the death of the animal. Correspondingly, patients have been observed at autopsy who have apparently recovered from extensive infarctions of the heart muscle. There is a slight anastomosis among the branches of the coronary arteries, so that these can no longer be considered end-arteries in the strictest sense of the term. The anastomosis, however, is insufficient to establish a collateral circulation if an area of any magnitude has been deprived of its regular blood-supply. An area so affected undergoes anæmic necrosis. In general, therefore, we may say that the occlusion of a coronary vessel of any magnitude is a matter of serious import.

Marked general anæmia also injures the heart, either by causing degeneration of its muscle-fibres, or by lowering their nutrition in some other, less obvious manner. General bodily malnutrition exercises a similar unfavorable influence upon the strength of the cardiac muscle, especially if the latter is otherwise subnormal, though symptoms are lacking. It is comparatively unimportant whether the malnutrition arise from poor food, gastro-intestinal disease or infectious processes.[86] In regard to infectious diseases, however, we must remember that they may injure the heart in a variety of other ways, as by causing myocarditis, or through the direct action of their toxins. The symptoms which arise under these circumstances are irregularities of rhythm and, especially, those disturbances referable to a diminution in the heart's capacity for work.

A fresh inflammation of the heart, whether of the endocardium, myocardium or pericardium, is injurious to the heart's activities. In many cases there results an actual loss of contractile tissue. As we have already mentioned, such changes not infrequently affect hearts which are already hypertrophied. They also occur, however, in previously normal hearts, especially from the general infectious diseases, such as acute articular rheumatism, diphtheria, typhoid fever and scarlet fever. Such an infectious myocarditis may develop at the height of the disease, or it may not develop until some weeks after the fever has disappeared, as happens especially after diphtheria and typhoid fever.[87]

Significant, in addition to the severity and

the extent of the myocardial changes, is their location. Attention has already been drawn to the fact that a small lesion situated in an important area may entail more serious consequences than a larger one located elsewhere. The discovery of the cardiac conduction path, made up of a specialized muscular tissue and of relatively limited extent, has taught us the location of such important areas. The literature is rich in observations concerning anatomical changes in the various parts of this system, which originates in the Keith-Flack node, at the mouths of the great veins, and which traverses the auricle to the node of Tawara, whence it is distributed by the bundle of His and its two main trunks with their ramifications to all parts of the ventricular walls. In a way, this peculiar muscle path possesses a pathology of its own.[88] It takes no part either in the hypertrophy or in the atrophy of the remainder of the myocardium; and it is endowed with an independent blood-supply. Furthermore, it may independently be the site of fatty and inflammatory changes and of tumor growths. The significance of these isolated changes in the causation of sudden death (heart-block) is still a matter of controversy.[89]

(Lewis[90] has reviewed about fifty cases of clinical heart-block, in none of which did a histological examination of the His bundle and its branches fail to reveal pathological changes. On the other hand, no case is on record of a complete destruction of the bundle in which just prior to death conduction was normal. Yet the presence of any lesion of the bundle short of a complete break in continuity served in no way as an index of the functional disturbances that may have been present intra vitam. In some instances, with extensive structural changes in the bundle, or in one or both main trunks, the degree of clinical dissociation may have been slight or transitory; while in others with complete dissociation, the bundle changes were less in evidence than in hearts exhibiting no clinical manifestations at all.—Ed.)

In other respects, what has been said concerning the remainder of the cardiac muscle, applies equally well to this specialized system.

Numerous poisons may depress the activities of the heart, in some instances after a primary stimulation, as occurs with digitalis and muscarin. It is possible that similar poisons are generated in the metabolism of the body. We know of at least

one disease in which the heart changes are probably due to such a cause, viz., hyperthyroidism.[91] There is here an increase in the rate and in the force of the heart's contractions. In many cases, an hypertrophy of both ventricles develops, and not a few of the patients die with the signs of a cardiac insufficiency. At autopsy hypertrophy and dilatation of the heart are present, but no characteristic changes are found in the cardiac muscle.[92] Since the blood-pressure in these cases is not always higher than normal, we might attribute the hypertrophy to the more rapid and forcible heart action, whether produced by nervous or toxic influences.[93] It is possible that the cardiac disturbances of certain individuals with struma may be due to an associated tracheal stenosis. But such a factor must be distinctly subordinate to the toxic action of the glandular secretion.[94]

The toxins produced by bacteria may likewise injure the strength of the cardiac muscle. This has been proved beyond question in the case of diphtheria toxin,[95] and is probably equally true of others.

It is difficult to say to what extent degenerations of the cardiac muscle injure the activities of the heart. Where they are very extensive, there can be no doubt that they cause serious disturbances. When, for example, in phosphorus poisoning, the ether extract amounts to twenty-six per cent. of the dried muscle, instead of the normal eleven per cent., and when microscopic examination shows that nearly every fibre is filled with fat droplets, a diminished capacity for work is to be expected. We are not yet able, however, to estimate the effect of the slight and of the moderate grades of fatty or of hyalin degeneration. It is customary to attribute cardiac weakness to these conditions. Yet we know that the degenerations may be found in apparently strong as well as in weak hearts.[96] Furthermore, it is possible that the cause of the fatty degeneration may itself independently weaken the cardiac muscle. Brown atrophy has hardly any clinical significance; and we are not yet able to say what functional effect is produced by fragmentation of the cardiac muscle.

The so-called fatty heart[97] remains to be considered. This term has been applied to two separate conditions—fatty degeneration of the muscle fibres, and excessive fatty infiltration into the interstitial tissue. The two affections have apparently

nothing to do with each other; and fatty degeneration rarely occurs to any marked degree in hearts which are the seat of fatty infiltration. The latter are usually associated with a general lipomatosis, and it is to them that the term fatty heart is more commonly applied. It is uncertain how much this excessive fat about the muscle-cells injures their functional activity. The muscular tissue is often surprisingly reduced in such hearts, probably from the pressure of the fat; possibly, however, because the atrophy of the muscle is primary, the infiltration of the fat secondary (*cf.* progressive muscular dystrophy). The disturbances of function in such hearts are probably due to the small amount of cardiac muscle present, relative to the total body weight. In other cases coronary sclerosis or an overindulgence in wine or beer constitutes the cause of the cardiac weakness.

Finally, there is a group of cases exhibiting weakness of the heart which falls into the class of so-called functional disturbances. Such a term simply means that at present we are ignorant as to the cause of these disturbances. The number of cases included in this group will progressively diminish as our knowledge increases. At the present time we must place in this category many of those cases of hypertrophy in which the demands so increase that the heart is no longer able to meet them, as well as many cases of heart weakness resulting from disturbances of the general nutrition. Many of the apparent nervous derangements must likewise be placed in this group.

Fatigue of the heart is just as little understood as is fatigue of the skeletal muscles. We speak of fatigue when the strength of a muscle diminishes as the result of exercise, and is recovered after a period of rest. If the heart be diseased, it is fatigued by a smaller amount of work than is the normal organ, and not infrequently it recovers slowly or not at all.

If sudden excessive demands be made upon a normal heart, it usually becomes fatigued, and after a rest it recovers. There have been cases described, however, in which a heart, as the result of a brief but excessive amount of work, was said to have been permanently injured, or, indeed, to have given out entirely. This has been looked upon as due to an excessive dilatation of the heart.[98] We know that such an acute dilatation, with an arrest in diastole, may be produced in animals by greatly increasing the resistance against which the heart must

pump. The possibility that a similar result may occur in man from excessive exertion cannot be denied absolutely. Yet the probabilities are entirely against this view. In the reported cases of heart-failure following exertion, too little attention has been paid to the condition of the heart muscle, which has, in most instances, been previously damaged.

There is no doubt that the diseased heart is not only easily fatigued, but that it is especially liable to become overdistended. When a convalescent from typhoid fever or diphtheria drops dead after some unusual exertion, it is usually from this cause. It is probable that fatigue or acute dilatation of a slightly damaged heart frequently occurs without recognition; and there always exists the danger that too much will be demanded of such a weakened heart.

The influence of the nervous system upon the heart remains to be considered.[99] It is theoretically possible that gross or microscopical lesions of the central nervous system should exercise an unfavorable influence upon the heart's activities because they injure the centres which regulate the organ, yet we have at present no direct evidence to prove that an injurious effect is actually produced in this way.

The central nervous system does in certain cases influence the heart unfavorably, but it is through so-called psychic influences, which are of quite a different nature. It is well known that sorrow, worry and care may affect the heart, not only in its rhythm, but in its strength.[100] This is frequently observed in those suffering from heart disease, but it may occur also in healthy individuals. Indeed, the depression of the heart's activities may be so extreme as to terminate fatally.[101] Neurasthenics frequently suffer from distressing cardiac sensations, from irregularity of the heart's action and even from cardiac weakness.[102] This last, however, is not common, and it is more frequently a part of a general muscular weakness.

(In certain forms of heart-block, however, vagus influences seem to play an important rôle in cardiac function. According to Lewis,[103] the vagus action in these cases is merely that of bringing into being, or intensifying the existing clinical manifestations, of an anatomical disturbance of the His bundle. The action of the vagus is observed also in the so-called sinus arrhythmias.—Ed.)

Many are inclined to refer various disturbances of the heart's function to disease of the nervous mechanism situated within the heart itself, but we are without any exact knowledge on this subject.

Cardiac weakness is ordinarily regarded as a weakness in the contractile power of the heart. Yet disturbances in the dilatation of the heart might almost equally well lead to serious consequences, for diastole is not merely a passive process. There is probably an active dilatation at the beginning of diastole,[104] and toward the end there is a rapid increase in the tension of the muscular wall which limits the degree of filling of the ventricle. If these acts are improperly performed, serious alterations in the circulation would result; the effects of such disturbances will perhaps play an important part in the heart pathology of the future. At present, however, we are quite ignorant of their practical significance, though Brauer is of the opinion that certain of the manifestations of an adhesive mediastino-pericarditis and the gallop rhythm of contracted kidney are due to some such disturbance in the dilatation of the heart.

Results of Cardiac Weakness.—In the consideration of the effects of cardiac weakness upon the circulation, it is immaterial whether the heart is primarily weakened so that it is unable to fulfil the ordinary demands of the circulation, or whether the demands are so increased that they become excessive.

Even the healthy ventricle does not expel the blood completely when increased quantities must be pumped with each contraction. If the auricle weakens, it soon ceases to contract, especially if it be distended. This has been observed experimentally and clinically.[105] If the ventricle be weakened, it does not contract so completely as does the normal one, and a smaller amount of blood than usual is expelled at a reduced speed. The aorta is less completely filled, and the arterial pressure sinks. The flow of blood into the ventricle is impeded, for not only is there less available space in the ventricle owing to the incomplete expulsion of blood, but the suction of early diastole is also probably weakened. The result is that the veins become distended, and the venous pressure increases.

The effects are best studied in those cases in which both ventricles are equally or nearly equally affected, which is, indeed, the commonest form

of cardiac weakness. The insufficiency of the left ventricle lowers the systemic arterial pressure, while the insufficiency of the right ventricle increases the pressure in the systemic veins. The difference in pressure between the veins and arteries, therefore, is less than it is normally, and consequently the rate of flow in the capillaries is lessened. At the same time, the distribution of blood is affected, for the arteries contain less, the veins more, blood than normal. Thus the result of a weakening of both ventricles upon the greater circulation is a diminished arterial pressure, an increased venous pressure, a diminution in the rate of blood-flow and an overfilling of the veins with blood. Somewhat similar conditions result in the pulmonary circulation; in the final analysis, the amount of blood in the latter will depend upon whether the right heart or the left is the weaker.

If only one ventricle be weakened, or, as is more frequently the case, if one be decidedly weaker than the other, then the effects are quite different. Let us first consider the consequences of a weakened left ventricle. This leads to a lower pressure in the systemic arteries and consequently to a slower rate of flow in the capillaries. The venous pressure in the pulmonary system is increased, and this leads to increased pressure in the pulmonary arteries, which necessitates more work for the right ventricle, as we have already explained (p. 19). Although the flow of blood through the lungs is maintained as well or nearly as well as before, yet the pulmonary vessels are overfilled and this is not without its effect upon the interchange of gases in the lungs (p. 34). Furthermore, these pulmonary changes react upon the general circulation, for the intrathoracic pressure is increased, and this lessens the aspiration of the blood from the great veins. In this manner an uncomplicated weakness of the left ventricle may cause stasis in the veins of the general circulation. In practice, such a stasis is greatly favored by the fact that nearly every case of weakness of the left ventricle is associated with more or less weakness of the right.

It may be asked whether it is possible for the right ventricle to pump its regular quota of blood if the left is only pumping a part of what it should. Such a condition would ultimately lead to an accumulation of all the blood of the body in the lungs. If life is to be maintained, a stationary period must develop in which both ventricles pump equal amounts of blood. But during the

time that it is developing, there is a gradual accumulation of blood in the lungs, so that in the fully developed condition there is an abnormal distribution of blood, more being in the lungs and less in the general circulation, even though both ventricles are now pumping equal amounts.

If the right ventricle is insufficient, less blood is sent into the pulmonary arteries, the pulmonary pressure falls, and the rate of flow in the lungs is diminished. Less blood is taken from the great veins of the general circulation, these become swollen, and all the organs, especially the liver, become hyperæmic from the venous congestion. The blood-flow in the general circulation is retarded, chiefly because the left ventricle cannot pump more blood than is furnished to it by the weakened right ventricle.

As a matter of fact, cases in which one ventricle alone is weakened are extremely rare. Most injurious agents affect both sides of the heart. Diseases of the lungs, however, affect chiefly the right heart, while arteriosclerosis and aortic insufficiency lead to disease of the left. In these conditions, therefore, we are most likely to see pathological pictures corresponding to those just described as characteristic of weakness of only one ventricle. In all cases, the blood flow is retarded and there is labored breathing on account of the lessened amount of blood which traverses the lung in a unit of time. The disturbances of breathing are greater when the left ventricle is weakened, because this causes in addition a passive hyperæmia of the lungs; whereas when insufficiency of the right heart exists alone, the blood tends to collect in the systemic veins without producing a pulmonary congestion.

Of the harmful effects resulting from cardiac weakness, the most serious is unquestionably the slowing of the blood-current; next to this is the change in blood-pressure. We are accustomed to regard the latter as the more important, perhaps because estimations of the blood-pressure are made with comparative ease. Yet, in the last analysis, the rate of blood-flow is of greater importance. This rate is, of course, largely dependent upon the arterial pressure, owing to the narrow range within which the venous pressure varies. (No deductions as to the rate of

blood-flow can be made from the systolic arterial pressure alone, for with the same pressure the flow may vary enormously, depending upon the amount of resistance which it encounters in the smaller arterioles—the so-called diastolic pressure. The ease and the comparative accuracy with which the latter can now be estimated have led to numerous studies relative to its significance. As an index of circulatory conditions, the diastolic pressure is not subordinate in importance to the systolic; and possibly it is greater. This subject will be referred to again.—Ed.) Nor can we say that the higher the arterial pressure the more favorable the condition, for a diminution under certain conditions is of distinct advantage, and a great increase brings with it certain dangers. On the other hand, the lowering of pressure must not be excessive, for a certain arterial pressure is absolutely necessary to maintain the rate of blood-flow essential for the proper performance of the functions of the body.

Disturbances of the heart's strength lead to its enlargement through a dilatation of its cavities. The weakened ventricle is unable to empty itself as completely as does the healthy one, and a certain amount of blood is left in it at the end of each systole. In diastole, likewise, it contains more blood than normal. There is, therefore, a dilatation of the ventricular cavity, and physical examination demonstrates an enlargement of the area of cardiac dulness. This dilatation of stasis must be sharply distinguished from the compensatory dilatation which we have already described in connection with certain valvular lesions. The latter are hardly pathological, for they are necessary in the accommodation of the heart to the new circulatory conditions. Only by a compensatory dilatation of this sort is the heart enabled to maintain a proper circulation in such valvular affections as aortic insufficiency (see p. 12). The dilatation which we are here considering is *not* of a compensatory nature, and it occurs only when the heart is unable to do its work. Although the normal heart does not empty itself completely when very large amounts of blood must be propelled, yet it soon regains its usual condition after the extraordinary demands have passed. In a case of pathological dilatation, however, a complete systole never occurs, and the cardiac chambers are constantly overfilled.

This dilatation of a weakened heart may arise from many causes. A heart may be unable to maintain the cir-

culation even when the body is at rest, in which case it is in a state of continual dilatation. On the other hand, the insufficiency may develop only when some extraordinary demands are made upon the heart; in this case the dilatation is temporary. Hypertrophied hearts are especially susceptible to dilatation. They may maintain the circulation for years, in spite of the extra work necessary, but finally injurious influences weaken the muscle, or the work to be performed gradually increases beyond the capacity of the heart, and dilatation follows. Frequently, hypertrophy and dilatation develop together. This occurs when, at the same time, increased work is necessary and injurious influences act on the cardiac muscle. The ultimate outcome of such a case depends upon the relation between these two factors. If the hypertrophy be in excess, the prognosis is comparatively good, whereas if the dilatation preponderate it is comparatively bad. A dilated heart may gradually strengthen and hypertrophy, so that it will accommodate itself to the increased amount of work necessary.

One effect of the poor circulation is a deficient supply of oxygen to, and an imperfect removal of carbon dioxide from, the tissues. The lessened blood-flow in the lungs also diminishes the interchange of gases there. The patient feels that he needs more air. The lack of oxygen and especially the presence of carbonic acid gas in the blood stimulate certain cells of the medulla oblongata, and this stimulation causes more frequent and deeper respirations. (See Dyspnœa, in the chapter on Respiration.) The increase in respiratory movements may partly compensate for the slower blood-flow, but it does not do so wholly. An added unfavorable factor in these cases is the marked predisposition to bronchitis and pneumonia.

The stasis of blood in the veins of the general circulation is very apparent. The superficial veins are enlarged and tortuous, and many, not before visible, appear. The poorly aërated blood gives a bluish tinge to the skin, which is usually most marked in the nose, ears, cheeks, fingers and toes, probably on account of the relative coolness of these parts.

The highest grade of cyanosis without a correspondingly great cardiac insufficiency is seen in congenital defects of the right heart (morbus cæruleus). The fingers acquire a characteristic club-shape, owing to nutritional changes in the

bones, and these, with the broad, dark-blue finger-nails, present a very characteristic appearance. It is difficult to give an adequate explanation of this cyanosis of congenital heart disease. A number of factors probably combine to bring it about. In the first place, owing to the inability of the right ventricle to compensate completely for the defect, there results an insufficient æration of the blood and a stasis—the latter being evident from the tortuosity of the veins of the skin and of the ocular fundi. In the second place, a defect in the ventricular septum, so commonly associated with congenital lesions, allows the arterial and the venous blood to mix. Finally, the well-known increase in the number of red blood-corpuscles in a unit-volume is probably an important factor, which may account for certain cases of cyanosis that cannot be explained in any other manner.

The venous hyperæmia causes a swelling of distensible organs. The kidneys become enlarged and dark blue, and their secretion is altered in a characteristic manner. The liver becomes swollen, hard and tense, producing a distressing feeling of pressure in the abdomen, or, indeed, actual pain. The plasma escapes from the capillaries into the subcutaneous tissues, causing œdema; and transudation into the serous cavities may also take place.

If the veins are much swollen, they frequently exhibit pulsations synchronous with phases of the heart-beat in addition to those of respiratory origin. These pulsations[100] are most marked in the jugulars, but they may be present in the veins of the upper extremity or of the chest wall. We distinguish two types of venous pulsation. The first is due to an insufficiency of the valves of the affected veins, which allows the pulsations normally present in the superior vena cava to be conducted to the peripheral veins. Such a normal or negative venous pulse arises from a hindrance to the venous flow of blood caused by each contraction of the right auricle. The vein is most distended during auricular systole just before the contraction of the ventricle. Tricuspid insufficiency produces a venous pulse of a totally different character. Here, the vein is distended by the blood which regurgitates from the right ventricle through an insufficient tricuspid valve, and the greatest distention occurs synchronously with or just after the ventricular systole. This is

called a pathological, or positive, venous pulsation. Without the aid of accurate tracings, it is often extremely difficult to determine which form of pulsation is present, owing to the irregular heart action and to the dyspnœa.

A positive venous pulse, though especially characteristic of tricuspid insufficiency, occurs also in that type of cardiac arrhythmia known as perpetual irregularity (arrhythmia perpetua), which is dependent upon a disturbance of the rhythmic beat of the auricles. The musculature of the latter either shows no evidence of contractions, or is in a state of fibrillation (see p. 66). The venous pulse, therefore, fails to portray the oscillation due to the contraction of the auricle, while during ventricular systole there exists a pronounced hindrance to the flow of blood from the great veins. The resulting systolic wave in the venous pulse is naturally not so marked as in the case of tricuspid insufficiency. A pathological venous pulsation may occur also when extrasystoles arise in the junctional tissues (atrio-ventricular extrasystoles), and occasionally in paroxysmal tachycardia (see p. 56).

(Mackenzie[107] formerly was of the opinion that auricular fibrillation was due to the fact that the inception of cardiac rhythm was transferred from its normal position—the sinus node—to the auriculoventricular node of Aschoff-Tawara. He applied to this condition, therefore, the term nodal rhythm, explaining in this way the apparent synchronous contractions of the ventricle and auricle, and the positive venous pulse. This conception of the nature of auricular fibrillation has been completely disproved by electrocardiographic studies, and is no longer held even by Mackenzie.—Ed.)

Disturbances of the Heart-Rate.—Disturbances of the rate of the heart may be due to a weakening of the organ, or may be independent of a diminution in its strength. The heart-rate varies greatly even in health.[108] It usually becomes slower with age, although in extreme old age it may again become more rapid. It is interesting to note that at this age the vagus tone is slight, or may be completely absent.[109] There are also great individual variations in the heart-rate; while some have a normal rate of fifty-six to sixty-eight per minute, others have a pulse-rate of seventy to eighty. As a rule, the rate is more rapid in women than in men. It is not our intention to name all those influences

which affect the rate of a normal heart. The mode of action of many is easily understood, whereas others have not yet been explained.

Physiological studies[110] have demonstrated that the contraction of the heart is initiated by a periodic stimulation of the fibres situated at the entrance of the great veins into the auricles. The impulse traverses the auricular muscle and is propagated via the bundle of His to the ventricles. The His bundle is a part of the so-called conduction path, a knowledge of which we owe particularly to Aschoff, Mönckeberg and their co-workers.[111] The bundle is made up of specialized muscle fibres (Purkinje fibres). Immediately above the auriculoventricular junction lies a denser accumulation of this specialized tissue, known as the Aschoff-Tawara node, which is unquestionably concerned in the coördination and rhythm of the ventricular beat. It is interesting to note that this node lies close to the point regarded by Kronecker as the cardiac centre of coördination.

From the Tawara node run fibres of a similar nature to all parts of the ventricles. A disturbance of the main trunk of the His bundle causes the ventricles to assume the rate peculiar to the isolated ventricle, *i.e.*, about thirty to the minute; unquestionably, however, the ventricles may have a higher automatic rate.

Near the entrance of the great veins into the auricles lies a similar mass of differentiated tissue—the Keith-Flack node. The evidence is still lacking to show that this node is of particular significance in the initiation of automatic stimuli from the sinus and auricles.[112] In the light of our present knowledge it seems more likely that all parts of the auricle are of equal weight in automatic rhythm inauguration. And, in all likelihood, even the propagation of the stimuli through the auricle is by the ordinary musculature.[113]

Though automatic stimuli may arise at any point in the myocardium, as Engelmann has always emphasized, those which are of auricular origin take precedence over the ventricular because of their more rapid inception. On the whole, the studies of Hering have led me to believe that we must return to the older view of the power of any part of the cardiac muscle to originate stimuli—a view which has been forced into the background by the prominence which has recently been given to the function of the

conduction path.[114] (Though observers are still not entirely in accord as to the rôle of the sinus node in the initiation of the normal heart-beat, yet the evidence favoring this view is considerable. Thus, artificial stimulation applied to the sinus node produces what may be called a normal electrocardiogram, whereas stimuli applied elsewhere cause atypical pictures. And the sinus tissue has been shown to be more irritable than that of the remainder of the auricle; while of the two auricles, the right begins to contract 0.01–0.03 second before the left.—Ed.)

The rhythm of a normal heart may seem absolutely regular to an ordinary observer, but more exact methods have shown that there are distinct physiological differences in the duration of the pulse-waves. According to Engelmann, the heart's action may be affected in various ways. There may be variations not only in the regular initiation of stimuli (chronotropy), but in the ability of the heart to respond to these stimuli (bathmotropy). Furthermore, the propagation of the stimuli over the heart (dromotropy), as well as the contractility of the muscle (inotropy), may be abnormally increased or diminished. The causes of disturbances of cardiac rate and rhythm may lie either in the muscle itself or in its nervous connections.[115] Thus we see how complicated are the conditions governing the rate and rhythm of the heart, and how difficult it must be to interpret the many clinical variations.

Though we shall not enter into the old controversy as to whether the heart-beat is neurogenic or myogenic,[116] it is interesting to note that the conduction system contains in addition to differentiated muscle-fibres, numerous ganglion-cells and nerve-fibres.

Rapid Heart Action (Tachycardia).—In certain conditions, the cause of an abnormally rapid heart action is clear. For example, atropin and similar drugs frequently increase the heart-rate by paralyzing the terminations of the pneumogastric nerve, although they can do this only in individuals in whom the vagus normally exerts an inhibitory action upon the heart. The same effect may be produced by pathological conditions of the vagus fibres or nuclei. Thus the rapid heart action which is so frequently observed at the end of meningeal inflammations is due to a vagus paralysis following

the period of vagus stimulation. Not infrequently a pulse-rate of 100 to 160 is observed in such cases, unassociated with any other cardiovascular symptoms.

It is more difficult to explain the rapid heart action due to exertion, which is so frequently seen in convalescents, anæmic individuals and in those who have heart disease. It is possible that there is here an increased irritability either of the heart itself or of its nervous connections, so that the chemical products of muscular activity produce an unusual effect upon these tissues.

Fever also causes a rapid heart action, for the increased temperature of the body stimulates both the central endings of the accelerator nerves and the heart muscle itself. If no other disturbing factors come into play, the rate of the heart increases proportionately to the rise in temperature. This parallelism between the temperature and the heart-rate is missed in certain infections. For example, in typhoid fever the pulse is relatively slow. With a temperature of 104° F. (40° C.), we may have a pulse of seventy or eighty. In scarlet fever, on the other hand, the pulse-rate is usually surprisingly rapid. In these diseases the action of toxins probably modifies the usual relation between the temperature and the pulse-rate.

A diminution in the arterial pressure is usually accompanied by an acceleration of the pulse. In many cases this is to be explained by the fact that there is a fall in cerebral pressure, which stimulates the central endings of the accelerator nerves. The purest example of this accelerating action is seen in the rapid pulse of widespread vasomotor paralysis (see p. 86). We frequently observe a rapid pulse in cases of cardiac weakness also, but in such cases it is uncertain whether the rapid heart action is attributable to the heart disease itself or to the fall in pressure. Experiments on animals would seem to indicate that an uncomplicated cardiac weakness leads to less frequent contractions, a fact favoring the hypothesis that the rapid action of the weakened heart is really due to the stimulation of the accelerator fibres occasioned by the lowering of the blood-pressure.

In hyperthyroidism, the tachycardia may be continuous, or it may occur in paroxysms. The symptoms of this disease are now attributed by many to an excessive thyroid metabolism, and it seems probable that the cardiac disturbances are likewise due to this cause (see Chapter VI). We are ignorant as

to which part of the cardiac mechanism is affected in these cases, whether it be the muscle, the cardiac ganglia or the central nervous connections.

The tachycardia of nervous people resembles that occurring in hyperthyroidism. Even in healthy individuals an increased heart-rate may be induced by various influences, as exercise, psychic disturbances and indigestion, but in nervous people the response to these influences is excessive. It is possible that the seat of the increased irritability is located in the cardiac muscle, for similar variations in rate are seen in those who suffer from disease of the myocardium, and in them at least there is no reason to assume that the condition is in any way dependent upon disturbances of the nervous system.

A rapid heart-rate may be produced by disease of various other organs of the body, such as the peripheral nerves (especially of the left arm), the lungs, the liver, the genitals and the gastro-intestinal canal. When the primary disease is cured, the cardiac disturbances disappear. Apparently such disturbances are due to reflexes from the diseased organs, a view which is supported by many facts. The patients are usually neurotic, the disturbances come and go in perplexing succession, and, furthermore, they usually arise from organs that are innervated by the vagus. For reflexes apparently occur most readily via nerves which carry both motor and sensory fibres.

The condition known as **paroxysmal tachycardia**[117] is characterized by an enormously accelerated heart-rate, which begins suddenly, lasts a short time and ceases as suddenly as it began. It may affect individuals with apparently normal hearts, or it may occur in those suffering from some definite cardiac disease. The duration of the attack may be minutes, hours, days or even weeks. The pulse-rate usually ranges between 150 and 300 per minute. The heart rhythm is regular and the sounds clear. The difference between the quality of the first and that of the second sound tends to disappear (embryocardia), a common phenomenon in any great acceleration of the cardiac rate. The pulse is small; oftentimes it cannot be counted. The blood-pressure is usually low, probably, because the shortness of diastole does not allow time for a complete filling of the ventricle. Wenckebach[118] has called attention to the fact that because of this short diastole, an auricular systole may coin-

cide with the ventricular contraction of the preceding heart cycle, thus obstructing the venous inflow, and accounting in all probability for the venous stasis. A ventricular venous pulse may also be present (see p. 52). The patient may or may not suffer from dyspnœa. The jugular veins are always swollen and usually exhibit marked pulsations. Other signs of venous stasis, such as swelling of the liver, albuminuria and even œdema, may develop.

Occasionally, even at the beginning of an attack, the heart is found to be enlarged; at times, however, it may be found smaller than normal. The apex beat is generally feeble, though the entire precordium may show a lively systolic quivering. Immediately after the attack the heart returns to its former size. Nevertheless, we have no right to consider this dilatation as the cause of the paroxysm, for it has been found absent in some cases, by the most careful observers. In my opinion, dilatation in these cases is an evidence merely of cardiac weakness.

An acute distention of the lungs has also been noted in certain cases at the onset of the attack, and the respiratory movements of the borders of the lungs have been diminished. To what extent these changes affect the heart is not definitely known.

Subjective symptoms are always present. During the paroxysm nearly all patients feel weak and faint, most of them suffer from dyspnœa, and some experience the sense of impending death. As a rule, the symptoms begin and end suddenly, frequently with peculiar sensations in the precordium; yet in some cases it is almost certain that the paroxysm may begin or end gradually.

During the interval between attacks the heart is often normal, so far as can be determined by physical examination. We should, however, be very cautious in our judgment of such cases, for it is difficult to exclude a coronary sclerosis, and many sufferers from this form of tachycardia are the subjects of easily recognized heart lesions.

The individual attack may begin spontaneously, or it may be precipitated by some unusual exertion, by excitement or by gastro-intestinal disturbances. These same causes normally lead to an acceleration of the heart's action, and it may be some-

what difficult to determine in the individual case whether the attack is really one of paroxysmal tachycardia or not.

We are still unacquainted both with the nature of paroxysmal tachycardia and with the cause of the individual attack. That nervous factors are of importance is evidenced by the fact that in certain cases pressure upon the vagus will end a paroxysm. (Pressure upon the vagus other than manual will also at times abort an attack; thus a similar effect may be produced by the swallowing of liquids with the head tilted far back (Herz), or by swallowing unchewed pieces of bread.[119]—Ed.) The etiology is unquestionably not a uniform one; in some cases the central nervous system seems to be at fault, psychic influences apparently precipitating the attack; while in others the disease appears to be of local nervous origin.

(Though there is a distinct nervous element in a great many cases of paroxysmal tachycardia, we are in a position to say, on the basis of electrocardiographic studies, that the condition is not, as was formerly believed, merely a neurosis. Many, if not most, cases represent a displacement of automatic impulse production from the normal place—the sino-auricular node, the "pacemaker" of the heart—to other parts of the myocardium. This new point of origin is oftenest, it would seem, in the auricles, though very rarely it may reside in the ventricles or in the junctional tissues.—Ed.)

It is likely that no single explanation will suffice for all cases.[120] Possibly in some, the basis is extrasystolic, because the paroxysm often seems to be precipitated by nervous influences and because the latter in turn frequently give rise to extrasystoles. According to A. Hoffmann, cases exhibiting an exact doubling of the normal rate suggest an extrasystolic character. Another theory is that the sinus node is unduly irritable. Or it is conceivable that this node normally initiates more stimuli than are represented by heart-beats; whereas in the tachycardial paroxysm each automatic stimulus is followed by an actual beat. (Sinus tachycardias usually begin and end gradually and are precipitated by excitement or over-exertion. They are observed as a rule in neurotic individuals, in whom insignificant causes are likely to increase the cardiac rate enormously. Alcohol, nicotin, bacterial toxins and fever may also be causative factors. In this type the pulse rhythm is normal,

and the electrocardiogram gives evidence that the contraction wave arises homogenetically, *i.e.*, in the Keith-Flack node.—Ed.)

Many unusual types of paroxysmal tachycardia have been recorded, such as exact doubling and quadrupling of the normal rate; while occasionally early in the attack a mid-wave is seen in the pulse-tracing, in which case it may be difficult to determine whether we are dealing with pulsus alternans or with a pulsus pseudo-alternans.

We shall return to this subject in our consideration of the cardiac arrhythmias (p. 62).

The effect of an acceleration of the heart-rate upon the circulation is variable. It may lead in the first place to an increased blood-flow; but, on the other hand, the shortening of diastole may cause an insufficient filling of the ventricles, with a consequent retardation of the circulation. Thus, experimental stimulation of the accelerator nerve produces more rapid and powerful cardiac contractions and an improvement of the circulation, whereas even the moderate acceleration caused by a vagus paralysis may lead to a slowing of the blood-current. A tachycardia may, therefore, affect the circulation of a patient in various ways, and numerous other factors must be considered in the individual case.

Slow Heart Action (Bradycardia).—A slow heart-rate may be due, in the first place, to a stimulation of the vagus nerve. We have an example of such an action in the slow pulse of asphyxia, in which the venous blood powerfully stimulates the central endings of the pneumogastric nerve. This tends in a certain degree to counteract the great rise in blood-pressure produced by the simultaneous constriction of the splanchnic vessels.

The central terminations of the vagus are also stimulated by any rise in the general arterial pressure.[121] The high blood-pressure in acute nephritis, for example, nearly always causes a slowing of the pulse. If the pressure rises gradually, however, and if it remains high for a long time, as happens in chronic nephritis and in some cases of arteriosclerosis, there is usually no reduction of the pulse-rate.

A rise in cerebral pressure will likewise stimulate the vagus, and we always find a slow pulse in those conditions which lead to a rapid increase of pressure in the cranial cavity,

such as intracranial hemorrhages and extensive meningitis. In such cases the vagus pulse is of great diagnostic significance. Even the gradual increase in the cerebral pressure that results from a brain tumor not infrequently causes a slow pulse.

Changes in the medulla, particularly in the region of the nucleus of the pneumogastric nerve, may lead to a marked slowing of the pulse and also to syncopal attacks. The similarity of this picture to that of complete heart-block has led some to refer the latter to such changes in the medulla.[122] This has no scientific basis, however.

The vagus may also be stimulated reflexly. The slow pulse observed at the onset of vomiting is caused in this manner; here the blood-pressure is probably lowered. This stimulation is usually due to a reflex from the stomach, although the vagus centre may be directly affected, as happens in the vomiting from increased cerebral pressure, or from the action of such drugs as apomorphin. Clinically, a reflex vagus pulse is frequently seen in the acute dyspepsias of children, in peritonitis, in strangulation of the intestines and in chronic constipation. In these cases there is often an associated arrhythmia.

Bradycardia may be produced by the direct action of certain poisons, as, for example, muscarin and the bile salts.[123] In the early stages of catarrhal jaundice, there is always a slowing of the heart-rate, and often irregularities of rhythm. In the chronic jaundice accompanying diseases of the liver itself, and in those associated with infectious diseases, the bradycardia is often absent, probably because smaller amounts of bile salts are manufactured, or because other factors influence the heart. Even in the marked jaundice of chronic obstruction of the common duct by stone or by tumor, there is frequently no slowing of the pulse. This is probably due to a diminished production of the bile salts; or possibly the body becomes accustomed to their presence. Experimental investigations have shown that the bile salts act both upon the central and the peripheral terminations of the vagus, as well as upon the cardiac muscle itself, particularly in the region of the sinus node. In catarrhal icterus, we cannot say at present which action is the most important. The hypothetical uræmic poison likewise slows the heart-rate, but we are ignorant of the manner in which it acts.

In all cases of continued vagus irritation the slowing of the pulse is only of moderate grade, rarely going below 44 to 48 per minute. The irregular pulse so frequently observed in these conditions well corresponds with the results of experimental stimulation of the nerve.

All varieties of bradycardia, other than those caused by vagus stimulation, are difficult to explain. A slow pulse may be present in neurotic individuals, but we are unable to say whether the immediate cause lies in some alteration in the nervous system, or in some changes in the heart muscle.

There is a group of bradycardias caused by changes in the heart itself. An increase in intracardiac pressure will cause a slowing of the heart-rate, as may be observed in cases of aortic stenosis and also, in certain instances, as a result of unusual, excessive exertion. In such cases the bradycardia is advantageous for it tends to lessen the work of the heart.

The bradycardias which follow infectious diseases are likewise due to changes in the heart. They are analogous to the subnormal temperature which is so frequently present under like conditions. The slowing of the pulse is most marked after pneumonia and typhoid fever. The injection of atropin does not stop the bradycardias of this type, nor may it affect them at all. Since atropin paralyzes the vagus terminals, and since the paralysis of these terminals does not materially affect the bradycardias under consideration, it must be inferred that they are due to changes in the cardiac muscle. Many would attribute this slowing of the heart to fatigue of the muscle, for there is usually an increased cardiac action during infectious diseases. It seems more probable, however, that post-febrile bradycardia is really an expression of cardiac weakness. We know that the weakened heart not infrequently contracts at a slower rate than normal. We also know that other signs of weakness are frequently present during convalescence, and that a cardiac insufficiency is especially prone to develop at this time.

The bradycardias which appear at the height of infectious diseases, especially that ominous slowing of the pulse during the course of diphtheria, are doubtless to be referred to changes in the cardiac muscle itself. Before they can be accurately classified, however, it will be necessary to determine their exact relation

to the various degenerations in the heart muscle which occur in these diseases. Anatomical changes in the myocardium may, as is well known, lead to a marked slowing of the pulse. This is seen in both acute and chronic myocarditis, as well as in the changes which follow diseases of the coronary arteries. A definite opinion as to how the bradycardia is produced in these conditions cannot be expressed without further observations based on the newer methods of study. Thus we must determine in how many of these cases the auricles and ventricles are beating independently, due to an interruption in the bundle of His. For there is little doubt that the latter is often affected along with the non-specialized cardiac muscle. This form will be considered under the arrhythmias (p. 67).

The bradycardia of the puerperium[124] is probably due to the decrease in the work of the heart which follows the delivery of the child, though an augmented vagus tonus must be considered in some cases.

We have already mentioned some of the effects of a slow heart action upon the circulation. The heart is enabled to recover itself during the lengthened diastolic pause, and its work is, to a certain extent, diminished. The velocity of the blood-current is lessened, yet this may be very slight if the slowing of the heart is only moderate in degree. If the bradycardia be due to vagus irritation, the individual contractions are not only less frequent, but they are less forcible, and the current may be slowed considerably. Whenever the bradycardia is extreme, the velocity of the blood-stream and the arterial pressure are always markedly diminished. Such patients cannot exert themselves without dyspnœa, and even when at rest they may suffer from syncopal attacks.

Disturbances of the Cardiac Rhythm.—We have already outlined the normal mechanism of the heart-beat (p. 53), a knowledge of which is essential to an understanding of the cardiac arrhythmias. Here our concern is only with those anomalies of the beat which are indicative of alterations in cardiac rhythm.[125] Though the arterial pulse, in rhythm and in frequency, corresponds for the most part to the heart-beat, this is not always the cause, for, on the one hand, the latter is not infrequently too feeble to evoke an arterial pulse, and, on the other, because of the unequal time consumed by strong and weak beats in reaching

the periphery, the pauses in the arterial pulse may be considerably longer than those between the corresponding heart-beats.

Extrasystoles (Premature Contractions).—One of the commonest causes of cardiac arrhythmia is the occurrence of extrasystoles, *i.e.*, contractions accompanying or superimposed upon the usual rhythm (pararrhythmia). The essential feature of this type is an irritable myocardium which initiates a premature contraction. Arterial hypertension is probably an important factor in some cases, for high blood-pressure by greatly increasing the tension of the muscle thereby renders it more irritable. Under these circumstances, only a slight added stimulus is needed to provoke the extra beat. In other cases, primary changes in the myocardium are at fault. Nervous reflexes, via the vagus, for instance, are very prone to excite premature contractions, though this has not been experimentally verified by direct stimulation of nerve trunks.

Extrasystoles may arise at various points in the heart-muscle—in the auricles, in the ventricles and in the sino-auricular and auriculo-ventricular nodes. The premature contraction generally follows closely upon a normal one. It is inferior to the latter in strength, partly because of the short diastole and partly because it falls into the so-called refractory period of the heart when the irritability of the latter is below normal. Obviously the shorter the pause between a normal beat and extrasystole, the weaker is the extra beat.

Following a ventricular extrasystole, with a pulse of average rate, the next normal systole drops out, because the stimulus which should produce it arises in the refractory period. The second normal systole, however, occurs in its proper place; and the interval between the normal beat before and after the extrasystole is exactly twice that between two normal successive contractions ("preservation of the physiological stimulus interval," Engelmann). If, however, the rate is abnormally slow, the correspondingly prolonged diastole allows of a full compensatory pause after the premature contraction, in which case the next auricular beat is likewise followed by a ventricular contraction (interpolated extrasystole).

The rhythm of the auricles is ordinarily not affected by ventricular extrasystoles, though occasionally the latter produce sec-

ondary, retrograde contractions in the auricles. The form of the auricular wave in such cases will depend upon the irritability of its muscle at the moment.

Auricular extrasystoles exert a variable influence upon the above-mentioned physiological interval between stimuli, *i.e.*, the compensatory pause, depending upon whether the extra beat originates nearer the venous or nearer the ventricular border of the auricle. Premature beats initiated in the sino-auricular node itself give rise to a complete compensatory pause, probably because the succeeding normal stimulus produces no contraction. Hence, the next auricular systole to appear falls approximately in its appointed place. The compensatory pause is incomplete, however, according to most observers, if the extra stimulus originates at a distance from the Keith-Flack node.

Not infrequently, the extra stimulus affects the auricle and ventricle simultaneously, producing the so-called auriculoventricular extrasystole. In this case, the auricles and ventricles contract synchronously (Mackenzie's nodal rhythm), or the ventricle may precede the auricle. In either case, the interval between the auricular and ventricular systoles (the a–c interval) is shorter than normal.

It is obvious that manifold disturbances of rhythm may be caused by these premature contractions, depending upon their point of origin and their arrangement, *i.e.*, singly, or in groups of two (pulsus bigeminus), three (trigeminus), etc. Though the study of these conditions has brought with it a great advance in our understanding of the arrhythmias, I feel that the tendency toward a subtle detail is overemphasized. A greater reserve would be well, in view of the complexities present, the meagreness of our present knowledge and the many interpretations possible in each case. Assurance often takes the place of exact knowledge.

As to the diagnostic significance of the extrasystolic arrhythmias, there is likewise little known. They may occur both in cases of myocardial disease and in conditions of nervous origin. Subjective disturbances, such as a feeling of anxiety, or an unpleasant palpitation, are often present, especially in cases on an apparent nervous basis. On physical examination, a loud first tone, similar to that in mitral stenosis and corresponding to the premature beat, is often heard. On the other hand, systolic mur-

murs which may have been present generally disappear, whether because of the shortened systole, or because of other intrinsic disturbances in the mechanism of the heart-beat, is not known.

Perpetual Arrhythmia (Auricular Fibrillation).—To those pulse irregularities due to a displacement of the automatic stimulus production from its normal position in the sinus node, Wenckebach has given the name true arrhythmias in distinction to the extrasystolic disturbances in which the abnormal rhythm runs side by side with the normal (pararrhythmias). In the severe cases of true arrhythmia the original rhythm is almost or entirely unrecognizable; contraction follows contraction with bewildering irregularity, even though the heart may be fully compensated. In some cases there is a positive venous pulse similar to that in tricuspid insufficiency (see p. 52). The oscillation in the jugular pulse due to auricular systole disappears as such and is replaced by a series of insignificant waves. This is the condition known as fibrillation of the auricles, which forms the basis of the clinical picture called perpetual arrhythmia, or pulsus irregularis perpetua. Cases have been observed in which the auricle returned to its normal contraction modus after the temporary disappearance of the fibrillation[126] (paroxysmal fibrillation).

The condition of the auricles in this disturbance is still not fully understood; possibly it differs in different cases. Observers have been of various opinions, some inclining to the belief that the auricular muscle is completely paralyzed, others that the auricles and ventricles contract synchronously, and still others that the auricular musculature is in a state of fibrillation. Though polygraphic and electrocardiographic studies do not warrant a definite interpretation of the phenomenon, we can say that the auricles are generally dilated.[127]

Perpetual arrhythmia is due either to an anomaly of stimulus production—a displacement, as noted above—or to a disturbance in the conduction of the stimulus from the sinus node to the auricles,[128] complicated by ventricular and perhaps by auriculoventricular extrasystoles. This conception of the origin of perpetual arrhythmia, though resting in some degree upon an anatomical basis,[129] must not be accepted unreservedly, for, as Aschoff points out, anatomical changes may be unsafe localizing

criteria. Especially does the significance of ventricular extrasystoles in the picture need further elucidation.

(Mention has already been made of the evolution of views as to the nature of auricular fibrillation (p. 52); how, at first, owing to the absence of the *a*-wave in the jugular tracing it was assumed that the auricle was in a state of paralysis—a view which had to be discarded because at autopsy the auricle was found to be hypertrophic; how, later, because of the frequently observed ventricular venous pulse, the idea was held that auricles and ventricles contracted simultaneously (nodal rhythm); and how, finally, by means of the electrocardiograph, it was demonstrated that the auricles were not quiet, but were giving rise to countless small waves, arising not at the normal place, but at innumerable points in the auricle.

Auricular fibrillation is to-day looked upon as one of the best-defined of the cardiac arrhythmias. Among its distinguishing features are its very frequent association with rheumatic endocarditis, particularly with mitral stenosis—a relationship, indeed, which was noted long before the significance of perpetual arrhythmia was understood; further, a ventricular pulse which is extremely irregular and usually rapid (unless a complicating heart-block be present); not infrequently the ventricular type of venous pulse, as already noted; and, finally, the almost specific response to digitalis.[130]—Ed.)

Pulsus Alternans: Hemisystoles.—In the case of two heart-beats occurring in quick succession, whether of extrasystolic nature or not, if the second beat be too feeble to produce a radial pulse, the possibility is present that the phenomenon is caused by a hemisystole, in which the two ventricles contract alternately, or there is an alternation between a contraction of the entire beat and that of the right ventricle. Such a regular succession of strong beats and weak beats has been observed in animals whose hearts have been injured. In this case we must assume either that the contraction-producing stimuli are alternately weak and strong, or that the heart responds with unequal strength to the same stimulus, or that regularly occurring inotropic variations are at work. A genuine pulsus alternans is not frequent in man; indeed many observers[131] believe that cases so diagnosed are in reality due to extrasystoles (pulsus bigeminus). Electrocardio-

graphic studies[132] have shown, however, that a true pulsus alternans does occur in man, while in animals it may be produced by the action of certain poisons. Pulsus alternans may be distinguished from extrasystolic bigeminy by the fact that the interval between the complete and abortive systoles in the former are generally equal. As the alternating pulse is due in all probability to variations in the contractile power of the heart it may be taken as evidence of cardiac insufficiency, and is usually regarded as of grave prognosis.

Heart-Block.—We have already described the path by which stimuli arising in the sinus node are propagated over the auricle to the node of Tawara and thence via the bundle of His to all portions of the ventricles; and we have noted that clinical heart-block is generally, if not always, associated with changes in this differentiated muscle-system (p. 42). According to the nature and extent of the underlying anatomical process, the disturbance in conduction may be partial (partial heart-block) or the pathway may be completely severed (complete heart-block).

In cases of incomplete block, the resulting manifestations are extremely variable. Thus a periodic retardation in conduction may cause a dropping out of single ventricular beats, due to the fact that the stimulus following the block finds the ventricle still in the refractory phase. A condition of this sort may occur both in toxic and inflammatory injuries of the His bundle. The greater the degree of the injury, the greater is the number of ventricular beats to miss. Vagus stimulation also has a certain bearing upon the dropping out of beats, though the modus operandi is not clear[133] (see also p. 45). Minor grades of disturbed conduction occur in various other conditions, especially in the infectious diseases and after the use of drugs such as digitalis.[134] In these last types, the auriculoventricular bundle is probably the point of attack just as in the forms mentioned above.

In cases of complete dissociation between auricles and ventricles, each contracts with its own inherent rhythm. That of the ventricles, in man, is ordinarily about thirty. According to Mönckeberg[135] this rate is probably found only when the main trunk of the His bundle is interrupted; whereas in disturbances in the Tawara node, the ventricles contract more frequently, though less often than the auricles. Digitalis seems

capable of increasing the automatic ventricular rate. (In incomplete block, on the contrary, digitalis is prone to cause a complete dissociation.—Ed.)

Animal experiments have shown that a partial heart-block can be made complete, the ventricles remaining motionless for a brief period during the transition. And in man, likewise, it has frequently been noted that the block may be incomplete at one time and complete at another.

The Adams-Stokes symptom-complex[136] has its anatomical basis in heart-block. Commonly arising in cases of coronary sclerosis and chronic myocarditis, its distinctive objective phenomenon is a marked bradycardia. Subjectively, the affected individual may be aware of no symptoms not dependent upon the underlying heart lesion; indeed it is noteworthy that many patients with an extremely slow pulse are in nowise handicapped as to occupation, ability to move about, and in general as to the enjoyment of life. In characteristic cases, however, there occur attacks of unconsciousness, associated apnœa and epileptiform convulsions. (It is to this type with bradycardia, syncopal attacks and epileptiform convulsions that the name Adams-Stokes syndrome is generally applied.—Ed.)

I am of the opinion that in many even of the so-called cardiac forms of the disease, cerebral changes play a part, for a quite similar picture may be observed, in the complete absence of cardiac pathology, in cases of cerebral arteriosclerosis. Nevertheless, I do not wish to minimize the importance of the very striking association of complete block and these peculiar attacks. Nicolai has recorded an interesting phenomenon in an individual with complete dissociation, in whom exercise not only did not accelerate the ventricular rate, but, on the contrary, slowed it.[137] Hoffmann[138] has frequently observed an acceleration of the automatic beat of the ventricles in cases of complete dissociation.

There are additional disturbances of heart-rhythm dependent upon anomalies in the properties of heart-muscle, viz., conductivity, contractility, irritability and automatic stimulus production, which, according to Engelmann, may occur independently of one another. To the many experimental studies and observations of Wenckebach and Hering we are indebted for a better understanding of the manifold pulse irregularities that may arise. At this point, we shall mention only the phenomenon

of grouped beats (Luciani) which has recently been observed clinically by Wenckebach. In my opinion, however, a certain reserve is still indicated in the interpretation of coupled beats, for there exists a peculiar innate tendency in this regard in the automatically beating ventricle, which would explain some of the bigeminal and polygeminal pulses in heart-block. In other cases, as already noted, bigeminy may be due to extrasystoles; while in still others it is the result of periodic disturbances of conduction. As Wenckebach points out, therefore, there is much included under bigeminy that belongs elsewhere.

Causes of Arrhythmia.—Myocardial disease is of first importance in the causation of disturbances of the cardiac rhythm. Inflammatory processes and infarcts resulting from coronary disease are more frequently the anatomical substrata of such arrhythmias than are the parenchymatous degenerations of the muscle. A diminished supply of blood to the heart may also lead to irregularity before the appearance of serious myocardial changes. As we have previously noted, there seems to be no definite relation between the extent of the myocardial disease and the degree of irregularity. The location of the process, however, is of paramount importance, as is evident from the results of lesions of the His bundle. Disease of the auricular musculature is especially apt to lead to irregularities in rhythm, according to many observers; yet our knowledge as to the importance of the auricles, and in particular of that area about the mouths of the great veins, in its bearing upon cardiac arrhythmia is still incomplete.

Cardiac irregularity may also occur without any demonstrable changes in the myocardium, as, for example, in cases of acute dilatation of the heart following excessive muscular exertion. To what extent nervous factors play a rôle in such disturbances of the rhythm is not known. The etiology of the so-called nervous arrhythmias is far from clear. Stimulation of the vagus, as we know, may lead to disturbances of conduction; and extrasystoles are especially frequent in neurotic individuals (see also p. 64). Respiratory variations in the frequency of the pulse are also particularly marked in such individuals. In these cases the pulse is accelerated at the beginning of inspiration and is retarded to such an extent during expiration that we can speak of an actual irregularity.

(This is one of the group of so-called sinus arrhythmias —all probably of vagus origin—and which Mackenzie has called the "youthful type" of irregularity.—ED.)

Reflexes may give rise to irregularities of the heart's action, as well as to tachycardia and bradycardia. We know that if the endocardium be touched during the course of an experiment, arrhythmia results. How important a part such reflexes play in clinical pathology is uncertain. Possibly the arrhythmia of endocarditis may arise from such reflexes; and possibly the arrhythmias sometimes seen in gastro-intestinal diseases are also of reflex nature. In both these examples, however, there are usually other factors present which might produce an irregular heart action.

Arrhythmia may be due to the action of poisons, notably of digitalis, caffein, tobacco and the toxins of uræmia. The relation of digitalis to heart-block has already been considered (p. 67). The irregular tobacco heart is well known. The toxins of infectious diseases, especially those of typhoid fever and diphtheria, may produce similar effects.

In chronic pericarditis and mediastinitis it is possible for the new-formed connective tissue to compress the aorta or the great veins during inspiration. This would lead to a diminution or disappearance of the pulse during inspiration (pulsus paradoxus).[139] Not every pulsus paradoxus is capable of being explained in this manner. It has been observed in simple insufficiency of the heart, and especially in association with stenosis of the larger air-passages, and under such circumstances the cause must lie in the heart itself.

The Cardiac Impulse.—If we inspect the chest of a normal individual, a periodic heaving is usually seen in the fifth intercostal space, median to the mammary line. This is called the cardiac impulse. It usually overlies the apex of the left ventricle, which is thrust into the intercostal space with each systole. During diastole, the heart is flaccid and tends to assume the shape given to it by its surroundings, but in systole it becomes rigid and assumes its own characteristic form. This throws the apex against the chest wall and is the principal factor in producing the impulse. The main part of the impulse occurs during the first period of systole at a time when all the valves are closed. The

heaving, however, continues a short time after the opening of the aortic semilunar valves.

Many factors may, therefore, affect the cardiac impulse, such as the position of the apex within the chest cavity, the force with which the heart contracts, and the condition of the chest wall and the overlying border of the left lung. Provided the latter do not play too disturbing a rôle, we may say in general that a powerful systole will produce a strong heaving impulse, and a weak systole will give rise to a small and soft impulse. It cannot be assumed, however, that an extensive, strong impulse is always due to a more powerful contraction of the heart-muscle.

A study of the apex-beat even by the ordinary methods of physical examination enables one to form a rough estimate of conditions in the heart, if he bears in mind the various factors which enter into the formation of the beat normally, and those which cause a change in its position, its breadth, its intensity, etc. Cardiographic tracings are necessary, however, to give us exact information about the apex-beat, though the value of this instrumental method is somewhat impaired by the fact that the characteristics of the beat vary considerably even in healthy individuals. Thus the cardiogram alone gives important information as to whether the apex-beat is formed by the left ventricle or right ventricle; while combined with tracings taken from the radial artery and jugular vein, the cardiogram serves as a valuable time-index of the different phases of the cardiac cycle. The bulk of our knowledge of the disturbances of heart rhythm was gained through the use of such simultaneous records of the movements of the ventricles and auricles (polygram).

The Heart-Sounds.—The heart-sounds may be altered either in their intensity or their character. One of the most important of these alterations is the increase in the intensity of the pulmonic or the aortic second sound. This accentuation is generally indicative of an abnormally high pressure in the corresponding artery. Since the pressure in the aorta is normally more than twice as great as that in the pulmonary artery, one might think that the aortic second sound would be normally much louder than the pulmonic second sound. Such is not the case, however. Examination of healthy individuals shows that there is but little difference between the second sounds in either intensity or character. As a rule, the pulmonic second

sound is relatively somewhat louder in childhood, but with advancing years the relation gradually changes until in old age the aortic sound is usually the louder. This relative weakness of the aortic second sound is due in part, at least, to differences in the structure of the aorta and the pulmonary artery.

We have said that, in general, an accentuation of a second sound indicates an increase of pressure in the corresponding artery. Yet we meet cases in which increased pressure is present without an accentuation of the corresponding sound; and, conversely, accentuation of the second sound may be present without any increase of pressure. Other factors must come into play. Of these the proximity of the vessels to the chest wall is unquestionably of importance. The physical condition of the arterial wall also influences the sound produced, and not infrequently we observe a loud, ringing aortic second sound in arteriosclerosis of the first part of the aorta, even though there is no increase of blood-pressure.

Accentuation of the pulmonic second sound is caused by conditions which lead to an increase of pressure in the pulmonary circulation. These conditions, which have already been enumerated (see p. 19) include mitral disease, weakness of the left ventricle, pulmonary emphysema, etc. The accentuation is ordinarily associated with an hypertrophy of the right ventricle, for both are caused by the increased pressure in the pulmonary artery.

Accentuation of the first sound is present in many cases of mitral stenosis, in which indeed it may be audible at some distance from the chest wall. The most acceptable explanation of this accentuated first sound is that it is due to a more rapid systole of the left ventricle, occasioned by the abnormally small amount of blood which this receives during diastole. The same factors underlie the loud first sound heard in rapidly beating hearts. Quincke has described abortive contractions of the heart which follow immediately upon normal ones in which a good filling of the ventricle was an impossibility and in which the systole was short. In these the first sound was often, but not always, louder than normal. The powerful contraction of an hypertrophied heart rarely produces a loud first sound, but usually an impure and muffled one. Weak and anæmic individuals, indeed,

frequently show surprisingly loud first heart-sounds, due probably to the associated tachycardia.

In certain cases, a doubling of one or other of the heart-sounds is heard, so that three sounds may be distinguished instead of two. This is most frequently due to a reduplication of the second sounds, which may sometimes be heard even in healthy individuals, more especially at the height of inspiration. It may also be present in various heart diseases, notably in affections of the mitral valves. This reduplication of the second sound is caused by a non-simultaneous closure of the two sets of semilunar valves. It may be conceived that the difference in the time of closure is due to an unequal duration of the right and left ventricular systoles, because one ventricle must do more work than the other. Such an explanation accounts very well for the reduplication in mitral valve disease. Why it should occur in normal individuals, and why it should be absent in cases where we have reason to believe that the systole of one side is lengthened, is not so readily understood.

A doubling of the second sound is frequently heard at the apex in cases of mitral stenosis. In this case the pause between the two second sounds is longer than it usually is between reduplicated sounds. Possibly the extra tone is in reality a rudimentary murmur, or is produced by the auricular contraction.

Reduplication of the first sound is less common than reduplication of the second. In place of a single first sound, we hear two, the second being, as a rule, the louder. This is considered ordinarily to be due to a non-simultaneous contraction of the two ventricles, but it must be admitted that the explanation is not beyond question.

In gallop rhythm[140] we likewise hear three heart-sounds instead of two, but the extra sound occurs at different times in different individuals. In some it is heard shortly before the first sound, being weaker and less ringing than this. In such cases it seems to be produced by the contractions of the auricle. We know that the auricular contraction does produce a tone, but that in health this so immediately precedes the ventricular sound that it is merged into it and only one sound is heard for both contractions. If a pause intervene between the two contractions, we hear two sounds, and this seems to be the explanation for one form of gallop rhythm. In the other form, the third sound occurs

shortly after the second, and it is then associated with a diastolic wave on the tracing from the cardiac impulse. Its exact cause is not settled, though there is some evidence that it is due to the ventricular diastole.[141] This second form of gallop rhythm is said to be more serious than the first. Gallop rhythm is a sign of cardiac weakness and is most frequently observed when an hypertrophied heart weakens, above all when the hypertrophy has been caused by nephritis. It may, however, result from arteriosclerosis, myocarditis or acute infectious diseases.

The quality or character of the first sound may change, but unfortunately the cause and the meaning of such changes are but little understood. A muffled or impure sound may be heard in the absence of any anatomical changes in the valves; but, on the other hand, such an impure sound may herald the onset of a valvular lesion. Many such changes are perhaps caused by some variation in the manner of the muscular contraction, or by changes in the tension of the valves.

The first sound may be fainter than normal, even though the ventricle is contracting powerfully; on the other hand, a faint sound may be due to a weakening of the ventricular contraction. I have observed a disappearance of the first sound in a case of typhoid fever in which at autopsy no macroscopical changes were found in the heart. In syncope, the heart sounds are often extremely faint; and since the pulse is also very weak, we must assume that a weak heart action is responsible for the faintness of the cardiac sounds.

Cardiac Murmurs.—If the auriculoventricular valves allow the blood to flow back into the auricles during systole, eddies are produced by the mingling of this stream of blood with the one coming in from the great veins. These eddies set the valves and heart wall in vibration very much as the violinist's bow causes the strings of the violin to tremble. Such vibrations of the valves give rise to the abnormal heart-sounds known as murmurs. A murmur of this type assists us in diagnosing a regurgitation through the tricuspid or mitral openings, as the case may be.

If the semilunar valves are insufficient, either because they are shrunken, or because the orifice is dilated, the murmur is produced in diastole, when the blood streams from the aorta back into the ventricle, and there causes the eddies which set the valves in vibration. The murmur may be heard throughout diastole

or it may be present only in the earlier part, at which time the negative pressure caused by the active dilatation of the ventricle most favors a return flow from the aorta.

An obstruction to the flow of blood through any of the orifices of the heart may also produce a murmur, and a simple roughening of the valves at the aortic orifice may do the same. The murmur caused by a stenosis of the mitral or of the tricuspid orifices is heard during a part or the whole of the diastole of the ventricles. When it persists throughout this period it is usually loudest at the onset and at the termination. The former accentuation is caused by the suction of the dilating ventricle, the latter by the auricular contraction. More frequently these murmurs are heard only during a part of the diastole, either at the beginning or at the end. The latter, called a presystolic murmur, precedes and merges into the first heart-sound, and is especially characteristic of mitral stenosis.

The murmurs produced by a narrowing or roughening of the semilunar valves are usually loud and rough. They occur at the same time that the blood is passing from the ventricles into the great arterial trunks. It is sometimes possible to demonstrate that they begin somewhat later than the beginning of the cardiac impulse, for it must be remembered that the first part of this impulse corresponds to that period of the ventricular contraction during which the intraventricular pressure is being raised to the level of pressure which exists in the great arterial trunks. For this reason no blood is leaving the ventricles during the first portion of the cardiac impulse, and consequently no murmur due to an obstruction at the aortic orifice can be produced at that time.

Murmurs vary greatly in intensity and in tonal character. Not infrequently they are distinctly musical, particularly when systolic. The cause of these variations in quality is not known.

In aortic stenosis the first sound may also disappear, not only over the aortic area, but at the apex as well. The left ventricle appears to contract without producing an audible first sound. This is probably due to the gradual and prolonged systole which is so characteristic of aortic stenosis. In aortic regurgitation the second sound may become very faint or it may disappear entirely.

Various opinions are held as to the cause of those murmurs which have been variously designated as **accidental, functional or hæmic murmurs.** They are usually systolic in time, and are

most intense in the second intercostal space to the left of the sternum and at the point of maximum cardiac impulse. It is quite certain that they are not due to an endocarditis affecting the mitral valves. We cannot exclude, with equal certainty, however, the presence of functional insufficiencies of the auriculo-ventricular orifice. Indeed, it appears to me that this is the cause of many of these murmurs. They are heard most frequently in weak and anæmic individuals, such as would be most liable to have a weak cardiac muscle, dilatation of the cavities of the heart, and functional insufficiency of the mitral and tricuspid orifices. We do not mean to imply, however, that all accidental murmurs are thus caused. Some, it may be, are due to anomalies in muscle contraction, or as Lüthje [142] suggests, to a physiological stenosis, as it were, of the pulmonary artery.

Palpitation.—Palpitation of the heart has been defined as an irregular or forcible heart action perceptible to the individual himself. In health, we are not ordinarily conscious of the action of our hearts, unless it is much increased by exertion or by excitement. It seems probable that there are sensory nerves in the heart or in its vicinity which are stimulated under these circumstances. Pathological palpitation may be due either to an abnormal heart action or to an increased irritability of these nerves, rendering the individual abnormally sensitive. Naturally, both causes may be operative in the same person.

An increased heart action does not necessarily produce the sensation of palpitation. This fact is frequently illustrated in cases of valvular disease, and is perhaps to be explained on the assumption that the gradual development of the condition allows the sensory nerves of the heart and adjacent structures to become accustomed to the changed conditions. Not infrequently, however, patients with hypertrophy and dilatation of the heart suffer from palpitation, especially during any exertion. In such cases the heart is working up to the limits of its capabilities, and possibly the increased tension of the cardiac wall stimulates the sensory nerves, and so produces the feeling of palpitation. This would explain why in stasis dilatation, in which the tension of the muscular wall is reduced, individuals often do not complain of palpitation.

In yet other individuals, no definite connection between the heart's action and the palpitation can be discovered. This is

especially true of the form associated with anæmia and that due to certain poisons, notably tobacco, tea and coffee. In such cases it is possible that the systole is modified, but it seems more probable that the patient is conscious of his heart's action merely because of an increased irritability either of the cardiac nerves or of their centres.

Cardiac Dyspnœa.—Shortness of breath is a very frequent symptom of heart diseases. It is often associated with a sensation of oppression in the chest, or with a general feeling of anxiety; but it may occur alone. It may vary greatly in degree, from the slightest dyspnœa on exertion to the most extreme air-hunger, even when at perfect rest. This symptom is not characteristic of any form of heart disease, but occurs whenever the interchange of gases in the lungs is seriously interfered with. Periodic interference with this interchange leads to periodic dyspnœa, the so-called cardiac asthma.

The dyspnœa of heart disease is always due to an insufficient interchange of gases between the blood and certain cells of the medulla (see Chapter IV). Two causes are directly responsible for the dyspnœa of heart disease. The first is the slowing of the blood-stream, which diminishes the interchange of gases in the lungs and in the respiratory centre of the medulla. Any slowing of the blood-stream in the lungs beyond a certain limit leads to an insufficient interchange of gases (see Chapter IV). A second cause for the dyspnœa of heart disease lies in the changes which take place in the alveolar epithelial cells of the lungs, and which lead to a rigidity of the pulmonary tissue.[143] These changes, which have already been described (see p. 34) would, undoubtedly, interfere with the interchange of gases in the lungs, even though the blood-stream were not retarded.

The dyspnœa which develops only when the patient exerts himself is due to a relatively slow circulation, the rate of flow not being increased proportionately to the demands for fresh blood. Indeed the exertion may cause a fall of arterial pressure in patients with heart disease.

The term cardiac asthma is applied to those paroxysms of extremely severe dyspnœa which occur in individuals who have heart disease. The dyspnœa is often of the most

extreme grade, and may be accompanied by excessive anxiety and a terrible sense of impending death. The paroxysms may begin after a meal, after exercise, during the night or without any apparent cause. They occur most frequently in those who have arteriosclerosis or chronic nephritis. During the attack, the pulse is usually rapid, soft and irregular in force and frequency. The blood-pressure is usually lower than normal, though in conditions of established high tension it usually remains above normal. The most frequent cause of cardiac asthma is a transient weakness of the left ventricle. This raises the pressure in the pulmonary vessels and so increases the work of the right heart. If the latter is unable to accomplish the additional work so thrown upon it, there results a diminution in the velocity of the general blood-current. In addition to this we have a widespread and sudden overfilling of the pulmonary capillaries which contributes toward the production of the symptoms. In certain cases, the dyspnœa becomes less when the right heart weakens. Since the pulmonary capillaries would then be less distended, this favors the view that the distention of the capillaries is to some degree responsible for the paroxysms of dyspnœa.

Patients suffering from heart disease frequently develop dyspnœa from pulmonary complications, such as bronchitis, pneumonia and œdema, to which diseases they are, indeed, peculiarly subject. In the French literature many other causes for the dyspnœa of heart disease are enumerated, among which are toxic and reflex influences. At present, however, there is little real proof of the existence of such causes.

Cardiac Pain.—As has already been stated, a feeling of intense anxiety often accompanies cardiac dyspnœa. This feeling may occur alone, or it may be associated with pain in the precordium. The latter, however, rarely occurs alone, except in nervous individuals, in whom the pain is of psychic origin and is simply referred to the periphery.

Cardiac pain, originating in the heart itself, is seen especially in disease of the coronary arteries and of the first part of the aorta. It accompanies aortic more frequently than mitral lesions, because the former are more often associated with arteriosclerosis. Patients with various forms of myocarditis also frequently com-

plain of pain about the heart and of cardiac distress, which may either be constantly present or may occur in paroxysms. Often there is no relation between these symptoms and the state of cardiac efficiency; generally, however, they represent a demand upon the heart for increased work which it cannot perform.

The severity of the pain varies greatly. On the one hand, the patient complains of sensations which trouble him mainly because they are unusual, while, on the other hand, the pain is of such indescribable severity that death seems imminent. It is not the place here to enter into a description of the clinical features of these cases of **angina pectoris.**[144] They occur, almost without exception, in those who have sclerosis of the coronary arteries. The attack may come on without any apparent cause, though usually it is precipitated by some unwonted excitement, by overexertion or by digestive disturbances. Most of the attacks are due to cardiac weakness induced by these unfavorable circumstances.

We do not know what causes the pain of angina pectoris. Arteriosclerosis of the coronary arteries is certainly present in most cases, frequently causing a narrowing of the lumen of the vessel. Perhaps it is the anæmia of certain parts of the heart which causes the pain. Such a theory finds an analogy in the condition known as intermittent claudication,[145] in which, owing to a narrowing of the arteries, pains and disturbances of function develop in the legs whenever the patient walks some little distance. In some cases the anginal paroxyms cease, and this has been attributed to a reopening of the vessel, although we have no proof for such an hypothesis. Breuer calls attention to the fact that we are not yet perfectly clear about intermittent claudication, for we do not know how great a rôle spasmodic contraction of the arteries may play in this condition. (Erb, who particularly studied this condition, finds excessive smoking a prominent factor in the majority of cases. Elimination of tobacco may bring about complete recovery, not only in intermittent claudication, but also in some cases of angina pectoris.—Ed.) Nothnagel believes that the pain may originate from the vessels themselves. Such an hypothesis, attributing the pains of angina directly to the spasmodically contracted vessel, is very attractive. It would explain the fact that the paroxysms of pain may occur without anatomical disease of the coronary vessels, as has been observed

in nervous individuals and especially in those who use tobacco to excess.

The anginal attack is often associated with a variably intense vasoconstriction of other parts, especially of the cutaneous vessels. Nothnagel has called this form **angina pectoris vasomotoria.** It may be present both in cases due to coronary sclerosis, and in those of purely psychic origin.

Many other questions in relation to angina are still unanswered, as, for example, the reason why the pains radiate to the left brachial plexus, the cause of the syncope in some cases and finally the cause of the sudden death. Every attack of true angina is a menace to the life of the individual, and not infrequently the patient dies during the attack. In only one other condition do we see an equally sudden death, and that is in coronary embolism. The body may be found in the exact position that it was in when the attack of angina began. No other signs of asphyxia are present. The cause of sudden death has never been explained.

The Arteries

The condition of the arterial walls and the width of the arteries exercise a considerable influence upon the flow of blood. If the arteries were all fully dilated, it would be absolutely impossible for the heart to maintain the circulation, for the relatively small quantity of blood in the body could not properly fill the vessels. The width of the arteries is regulated mainly by reflexes coming from various parts of the body; and by virtue of this regulatory mechanism the heart is enabled to graduate its own work. The condition of the vascular area under control of the splanchnic nerves is of prime importance in its effect upon the general arterial tension; though in man the cutaneous vessels constitute a not inappreciable factor.

If the arteries leading to a certain part of the body dilate or contract, the blood-supply to that part will be altered. These changes are fully discussed in the ordinary text-books on physiology and pathological anatomy, and need not be dwelt upon here. Our concern shall be with those disorders of vascular function which affect the circulation as a whole. An example of this we have seen in arteriosclerosis, which frequently causes an increase in arterial tension, particularly if it involve the root of the aorta

or the vessels of the splanchnic area. Furthermore, we have already emphasized the fact that hypertension on an arteriosclerotic basis is not purely of a mechanical nature, but is due, in large measure, to an altered vasomotor tonus. Indeed, it would seem that certain cases of high blood-pressure are the result of a primary augmentation of this tonus. These are the cases of so-called *essential hypertension*. What relationship they may bear to arteriosclerosis is not known, though it is possible that they are precursors. (But recent extensive studies[146] appear to indicate that a large proportion of such cases of idiopathic hypertension, especially those with a systolic reading of 180 mm. and over, are really due to anatomical changes in the kidneys, despite the fact that they do not betray themselves during life by urinary findings. Modern methods of determining the functional efficiency of the kidneys (see pp. 427, 430) promise much in the way of establishing the renal origin of such cases.—Ed.)

A widespread spasm of the vessel walls tends to raise the arterial pressure by increasing the peripheral resistance against which the left ventricle must pump. In cases of spasm affecting the numerous vessels under the control of the splanchnic nerves, the general pressure is also increased, but here the work of the ventricle is augmented by the fact that the volume of blood in the periphery is greater because of the emptying of the splanchnic vessels. Vessel-cramps of this sort are seen in cases of asphyxia and in poisoning due to strychnin and lead; and Pal[147] has emphasized their importance in other conditions. The cause of these so-called **vessel-crises** is but little understood. In some instances they are possibly of nervous origin; while in others they are of reflex nature, in which case they probably possess a regulatory function, and have an intimate relation to factors concerned in renal hypertension.

The Arterial Blood-Pressure.—The blood-pressure[148] in the larger arteries is dependent mainly upon two factors—the amount of blood pumped into the arterial system by the heart, and the resistance offered to the escape of blood from this system through the smaller arteries and capillaries. Of less importance are the elasticity of the vessel-walls and the total quantity of blood in the body. These various factors influencing blood-pressure may interact upon each other in the most complicated manner. For example, if the arterial pressure be increased from

any cause, the vagus nerve is stimulated, with the result that the heart is slowed and less blood is delivered into the aorta. In a like manner, when the volume of blood is rapidly changed, the blood-vessels change their calibre, so that, within certain limits, the blood-pressure is not altered.

Systolic and Diastolic Pressures. The Pulse-Pressure.—The arterial pulse is caused essentially by the variations of pressure within the artery, produced by the intermittent expulsion of blood from the heart. The highest point on this wave of arterial pressure is called the systolic pressure, and the lowest point the diastolic pressure. The difference between the two, *i.e.*, the variation of pressure with each pulse, is called the pulse-pressure. By means of the ordinary sphygmomanometer it is now possible to determine the diastolic pressure with almost as great facility and accuracy as the systolic. This has served as a strong stimulus to the study of the factors concerned in the production and in the variations of the systolic, diastolic and pulse-pressures and has necessitated a certain revision of ideas formerly held as to the significance of hypertension.

The diastolic pressure[149] measures the peripheral resistance and as such is probably a better index of the work thrown upon the left ventricle than is the systolic. This is all the more true, under given conditions, because the diastolic pressure seems to maintain a more constant level than the systolic, which, as is well known, may undergo marked and rapid changes, not only physiologically, but especially in cases of hypertension. The pulse-pressure represents the actual excess of pressure impelling the blood to the periphery, or the "load" which the heart must carry to maintain the circulation. Though observers are not in complete accord as to what constitutes a normal pulse-pressure, it may be said in general that a reading below 30 mm. Hg. is low and one above 50 mm. is high. Thus, in a case of hypertension, the outlook would depend not so much upon the systolic pressure, as upon the pulse-pressure, which must be high to maintain compensation. A rise in the diastolic pressure without a corresponding increase in the systolic in such cases would signify that the growing peripheral resistance is not met by increased work on the part of the heart, or in other words that the pulse-pressure was falling and decompensation was at hand.

The attempt has been made to correlate the cardiac out-

put per beat—the blood flow from the heart—with the pulse-pressure. In general, it is true that an increased systolic output produces an augmented pulse-pressure and *vice versa*. That there can be no absolutely definite ratio, however, between ventricular output and pulse-pressure is evident from the fact that the elastic integrity of the vascular wall and the fulness of the artery must be taken into consideration. In arteriosclerosis, for example, and in aortic insufficiency, the ratio of pulse-pressure to cardiac output behaves contrary to the general rule.

Physiological Variations in Blood-Pressure.—Age influences the blood-pressure. During infancy the systolic pressure usually ranges between 75 and 90 mm. of mercury; later, the weight and height of the child appear to be more influential in determining the pressure than is the age.[151] In adults, age and physical development, and to a lesser degree, sex are important. The systolic pressure increases slightly with each decade, ranging from 100–130 mm. in young adults to 130–145 mm. in old people. A pressure consistently above 150 mm. is pathological. Women show slightly lower systolic values than do men of the same age.

Excitement, anger and worry generally cause a considerable rise of pressure. Though the pressure increase due to worry is usually transitory, it is not unlikely that long-continued worry may lead to permanent hypertension. The question of the emotions and epinephrin discharge is considered in another place (p. 338). The effect of exercise is variable. Moderate exertion—as, for example, walking—may diminish the diastolic pressure and increase the pulse-pressure; severe exertion, on the contrary, tends to increase both the systolic and diastolic readings, indicative apparently of the increased cardiac activity. The effect of severe exertion is intensified if the act requires mental effort. An increase of 10 to 20 mm. generally accompanies the change from the recumbent to the erect position. This normal response to exercise and to a change in position has been made use of as a test of the functional efficiency of the heart, an inefficient organ frequently responding with no pressure rise and sometimes, indeed, with a slight fall. But as previously noted, the behavior of the diastolic and pulse-pressures in these cases would offer more valuable diagnostic criteria.

In the first two hours of undisturbed sleep, there may be

a fall amounting to 20 mm., while the maximum for the day is observed, as a rule, in the late afternoon.[152] Considerable study has been devoted to the effect of altitude and of low atmospheric pressures upon the blood-pressure.[153] Though some individuals exhibit no change under these conditions, the effect in general would seem to be a slight reduction, both in normal individuals and in those with hypertension.

In this connection may be mentioned also certain factors in their bearing particularly upon cases of high arterial tension. We have already noted that persons with high blood-pressure do well rather than badly in high altitudes, in so far as the pressure itself is concerned. Furthermore, recent work would indicate that a protein diet and a large fluid intake do not influence an uncomplicated hypertension unfavorably. Sweat baths generally cause a pronounced drop in pressure, which may persist for weeks; while carbon dioxide baths and the high frequency current have a similar, though less constant, effect.[154]

Pathologically Increased Blood-Pressure.—Emphasis has already been placed upon the importance of the nephritides in the production of continuous high pressure, whether the renal lesion be evident from the urine or not. Attention has been directed also to the factors which seem active in the causation of this form of hypertension, and in particular to mechanical and functional alterations in the arterial walls. The high pressure observed in arteriosclerosis, either generalized or involving particularly the first part of the aorta or the splanchnic vessels, and in the so-called vessel-crises, probably bears a close etiological relationship to renal hypertension. Interesting in this respect are the most recent studies of Pal[155] in which cases of high pressure seemingly due to an increased arterial tonus, *e.g.*, post-scarlatinal uræmia, and cases of more localized smooth-muscle spasm—angina pectoris, bronchial asthma and pylorospasm—yield to the action of papaverin, which is endowed with the property of relaxing smooth muscle.

Poisoning with strychnin and lead probably produces an augmented arterial tension, as previously mentioned, by causing widespread vessel-spasm. The effect of lead in this respect is seen also in its tendency to cause anatomical vascular and renal changes, and in its association with gout and diabetes.

The last diseases, however, may independently cause atheroma and hypertension. Experimentally, digitalis raises the arterial pressure by increasing the work of the heart and by causing vasoconstriction. In cases of hypertension, however, particularly when associated with cardiac decompensation, digitalis and allied drugs not only improve the circulation, but often cause a drop in pressure.[156] Epinephrin, in pharmacological doses, produces hypertension by constricting the peripheral vessels. The physiological action of epinephrin is discussed elsewhere (p. 338).

Acute asphyxia or acute anæmia of the medullary centres of the brain will stimulate the vasomotor centre most powerfully, producing a contraction of the splanchnic vessels and a great rise in arterial pressure. Such a cerebral anæmia appears to be the cause of the extremely high blood pressures sometimes seen in cases of acute cerebral compression, a subject which will be discussed in another place (p. 446). Lead colic is usually associated with high arterial pressure, and the early stages of peritonitis are likewise frequently accompanied by such a rise. Pain, even that caused by pinching the skin, usually increases the systolic pressure in healthy individuals.—Ed.)

The effect of an increased peripheral resistance upon the general circulation depends, for the most part, upon the behavior of the left ventricle. If this were to act in an ideal manner, it would contract more forcibly, and so, by raising the general arterial pressure, would overcome the increased resistance. Unfortunately, however, when the peripheral resistance and the arterial pressure are much increased, the left ventricle does not empty itself completely, the pressure in the left auricle rises, and a retardation of the blood-flow through the lungs occurs.

Pathological Diminution in Blood-Pressure.—Widespread dilatation of the blood-vessels may lead to a serious fall of arterial pressure and a slowing of the circulation, for, as we have said, the total quantity of blood in the body is insufficient to fill the blood-vessels properly if they are all widely dilated.

Such a widespread dilatation may result from a general loss of arterial elasticity with a stretching and widening of the blood-vessels. This has been observed in certain cases of aortic insufficiency (p. 35), and apparently in the late stages of arteriosclerosis (p. 22).

Arterial dilatation may also result from a widespread

loss of arterial tonus. Thus, if the splanchnic vessels lose their tone, they become filled with blood, and the arteries to the other parts of the body, especially to the skin and muscles, are left comparatively empty. The patient becomes weak and pale, the arterial and venous pressures fall, and the heart receives an insufficient supply of blood. The pulse becomes soft and rapid, and finally syncope supervenes. Such a patient is practically bled into his own abdominal vessels, and life may last only a few hours or even minutes. If other arteries in addition to the splanchnic vessels are dilated, the symptoms are intensified; yet the condition of the splanchnic vessels is of paramount importance on account of their great capacity.

A clinical picture, similar to that just described, may be produced by toxic doses of such drugs as chloral and alcohol, both of which will ultimately paralyze the vasomotor centre. A similar picture is also presented by the so-called collapse that sometimes occurs during the course of infectious diseases. These symptoms are not those of ordinary heart failure, for the pulmonary congestion and the stasis in the veins of the general circulation are both lacking. The picture seems rather to be caused by an insufficient supply of blood without stasis, and is fully in accord with the assumption of an extensive vasomotor paralysis.

This question has been carefully studied in animals.[157] The great falls in pressure which occur at the height of experimental infections with the pneumococcus, the diphtheria bacillus and the bacillus pyocyaneus, have all been shown to be due to a paralysis of the vasomotor centres. In pneumococcus infections, the heart may even beat with more than its usual force, and may thus, to a certain degree, compensate for the loss of vasomotor tone. So long as its structure remains intact it can meet the extra demands made upon it, such as the rise of blood-pressure caused by asphyxia. In diphtheria infections, however, the heart is usually also injured, and some, indeed, assert that the injury to the heart is here the more important cause of the circulatory disturbances.[158] It has also been definitely proved that in a perforative peritonitis experimentally induced, the cause of death is a toxic paralysis of the vasomotor and respiratory centres.[159]

The result of these animal experiments may be applied with all the more confidence to man for the reason that the clinical

picture of collapse corresponds so closely to what we should expect from a vasomotor paralysis. I have the impression that the most severe circulatory disturbances in these diseases are due to central vasomotor paralyses, preceded in many cases by local lesions of the blood-vessels.[160] As a rule, the heart[161] is also affected apart from the changes in the arteries and thus the circulatory apparatus as a whole is damaged. Sometimes, indeed, the cardiac weakness is more prominent than the vascular paralysis but in either case the therapeutic indication is to improve the circulation by strengthening the heart.

(Another form of extreme circulatory depression is that seen in **anaphylactic shock** (see p. 179). Animal experiments have shown that in this condition there is regularly a considerable fall in blood-pressure, which may amount to 20 to 30 mm. Hg. Though the splanchnic dilatation and medullary anæmia are probably the chief factors in the production of this form of shock, it would appear from electrocardiographic studies that the origin is partly cardiac.[162]

The cause of so-called **surgical shock** is still not definitely settled; and it is not unlikely, as Yandell Henderson[163] has stated, that the etiology is probably not uniform. In Crile's earlier publications,[164] shock was attributed to an exhaustion of the vasomotor centre caused by severe traumatism to the peripheral nerves. This in turn caused a fall in blood-pressure which was regarded as the essential feature of the picture, and to the correction of which remedial measures were directed.

Objection has been made to this theory because it seemed inadequate to explain all cases and also because there may be a considerable rise in pressure in the early stages of shock lasting until the vasoconstriction caused by the centripetal stimuli finally gives way to overstimulation and depression. And, more recently, Crile[165] has come to believe that the essential substratum of shock resides in specific changes in the brain-cells which bring about a conversion of the potential energy of these cells into kinetic energy. The direct cause of this change is ascribed by Crile to injurious stimuli (**noci impulses**), such as fear of the operation, fatigue, loss of sleep and those due to the anæsthesia itself, which so lower the cerebral threshold of sensitiveness as to render it susceptible to the trauma of the operation. The attempt is made, therefore, to exclude these noci impulses by eliminating, so far as

possible, the above mentioned psychic predisposing factors, and also the pain and trauma of operation by a perfect anæsthesia, both general and local. This method Crile has called **anoci-association.**

Henderson believes that certain cases of shock, at least, are due to **acapnia**—a deficiency of carbon dioxide in the blood—which occurs when various factors such as pain, trauma, exposure of the tissues, fever, faulty anæsthesia, etc., lead to an increased respiratory activity. This in turn causes a lowering of the osmotic tension of the blood, a loss of fluid from the latter and a diminution in the total volume of blood. The consequent fall in venous pressure deprives the heart of an adequate supply of blood which is evidenced by a diminished output in systole. Henderson's theory, therefore, postulates a condition not unlike hemorrhage.—Ed.)

A comprehensive and nice adaptability of the diameter of the arterial tree to the activity of the heart is of great importance in the maintenance of the circulation. An equal and perhaps greater factor is the balance between the volume of blood in one vascular field and that in others. Such an adjustment is essential not because the total blood mass must be properly distributed among the different vessels, but because correlated organs can thus receive a sufficient supply. Romberg and O. Müller[166] have shown that in arteriosclerosis the vascular reflexes are markedly disturbed. The same is true of those remarkable conditions of local anæmia, such as Raynaud's disease, which at present are regarded as of nervous origin.

The Veins

Venous Stasis.—It has already been shown that stasis of the blood in the veins may result from cardiac weakness. The stasis in the pulmonary circulation, produced by the weakness of the left ventricle, may be overcome to a certain extent by the increased activities of the right ventricle; whereas the stasis in the veins of the general circulation, resulting from a weakness of the right ventricle, cannot be thus overcome, and the entire blood current is slowed.

General venous stasis may also be caused by diseases of the lungs or by pressure upon the great veins. If the intrathoracic pressure be increased, either by a diminution in the elasticity of

the lungs (emphysema) or by a collection of fluid or gas in the pleural cavities, or if the thoracic movements are lessened, as happens during superficial breathing, then a diminution in the flow of blood to the heart results. Pressure upon the great veins by tumors and especially by pericardial effusions may also interfere with the return of venous blood to the heart. A pericardial effusion may, indeed, cause sudden death by compressing the venæ cavæ just before their entrance into the right auricle, and so shutting off the entire blood-supply to the heart.

Venous Murmurs.—In certain individuals, especially in chlorotic girls, a murmur may be heard over the bulbus jugularis. This is usually louder on the right than on the left side, and is known as the venous hum (bruit de diable). Its cause is not well understood. Some believe that it is a murmur of stenosis caused by the passage of the blood from the external jugular vein into the jugular sinus; yet why this should occur especially in anæmic individuals is not known. Sahli [167] considers that the blood flows more rapidly in anæmia, and that this is the cause of the murmur; and as the rate of flow in the anæmias appears to be more rapid than normal, this explanation seems the best at hand.

The Circulation of the Lymph

The lymph may be looked upon as the fluid that has escaped from the capillaries. It carries material to the cells of the parenchyma, and, laden with waste products, returns to the blood by way of the lymphatic vessels. Its composition, therefore, varies according to the organ from which it comes and according to the activity of that organ.

We know of no diseases in which too little lymph escapes through the capillary walls, although it seems probable that such do exist.

Œdema.—Certain conditions lead to an accumulation of lymph in the lymphatic vessels and spaces, among which latter the serous cavities may be included. Theoretically, such an accumulation may be brought about, first, by an excessive formation of lymph; secondly, by a hindrance to the escape of lymph; and thirdly, by a combination of the two. The quantity of fluid that passes through the capillary walls depends, on the one hand, upon the difference in

pressure between the blood in the capillaries and that of the lymph in the surrounding tissues, and, on the other hand, upon the permeability of the capillary walls themselves.

Œdema from Stasis.—Œdema may be caused by a stasis of blood in the veins. This stasis may be merely *local*, as when it is caused by an occlusion of a vein by thrombosis or external pressure; or it may be *general*, as when it results from pathological changes in the lungs, weakness of the right heart, intrathoracic tumors and pleural or pericardial exudates. The œdematous fluid that collects in the lymph-vessels and spaces in such cases is poorer in proteids and leucocytes, but richer in erythrocytes, than is normal lymph. The organs that become most swollen are those in which the tissues are under the least elastic tension, and in which the venous stasis is favored by gravity. For this reason the œdema caused by general stasis is usually first observed about the ankles and over the lower part of the back.

The mere obstruction of a vein does not necessarily lead to œdema, for a collateral venous circulation may be established. After the experimental ligature of a vein, the occurrence of œdema is greatly favored by the frequent accompanying arterial hyperæmia.

Even an increased transudation of lymph does not necessarily cause an œdema, for the excessive amount may be carried away by the lymphatics. There must be, in addition, therefore, some interference with the lymph-flow from the part. When general venous stasis causes the œdema, the blood-pressure in the left subclavian vein is naturally raised, and this would furnish the interference with the flow of lymph into this vein from the thoracic duct.

The lymph-flow may also be hindered in other ways. An increased pressure in the capillaries is transmitted to the tissues about them, which gradually become stretched and lose their elasticity. The loss of elasticity diminishes the pressure normally exerted by the tissues upon the lymph-spaces, the difference between the blood- and the lymph-pressures is, therefore, increased, and exudation is favored. On the other hand, the diminished pressure exerted by the tissues upon the lymph-spaces tends to lessen the rate of lymph-flow from the tissues toward the thoracic duct. For these reasons, *the elasticity of the tissues*

exercises a most important influence upon the occurrence of œdema and different organs become swollen to different degrees, even though they all are exposed to the same venous stasis.

The mere obstruction of a lymphatic vessel rarely leads to œdema, on account of the numerous anastomoses between the lymphatics. If, however, the thoracic duct be obstructed, ascites and œdema of the legs usually develop.

Inflammatory Œdema.—As is well known, inflammations injure the walls of the capillaries. There is an active local hyperæmia, and, at the same time, a slowing of the blood-current caused by the changes in the vessel walls. The latter influence the amount and character of the transudate, and consequently the lymph of inflammation differs from that normally transuded, in that it contains more albumin and more numerous blood-corpuscles. Purulent inflammations are characterized by the richness of their exudates in leucocytes, which are attracted thither by the primary cause of the inflammation.

Inflammatory processes also interfere with the removal of lymph from the tissues, for they directly diminish the tissue elasticity, with the results just described. Even the elasticity of tissues at some little distance from the inflammation may be diminished, so that these also become œdematous, thus producing the so-called collateral œdema.

Nephritic Œdema.—Of the dropsies that accompany nephritis[168] some are unquestionably due to simple stasis. We have seen that the heart is often weakened in nephritis, in which case it is obvious that we have to do with the ordinary dropsy of heart disease. Here, however, we wish to consider those nephritic œdemas that occur independently of any cardiac weakness. They usually appear first in the subcutaneous tissues, and especially in those that possess the least tension, as about the ankles and eyelids, though not infrequently the great serous cavities are early filled with fluid.

Œdema of this character is rarely seen in certain forms of nephritis, especially in contracted kidneys, in the nephritides caused by certain poisons (arsenic) and in those associated with certain infectious diseases (pneumonia and typhoid fever). On the other hand, œdema is common and often marked in chronic parenchymatous nephritis, in in-

flamed amyloid kidney, in scarlatinal nephritis and in primary acute nephritis. We are still in no position to state, however, whether the œdema in these cases is due to the anatomical lesion *per se* or to the consequent functional disturbance.

The urine in the dropsical cases is frquently diminished in amount and rich in albumin; yet the high percentage of albumin can hardly be the cause of the œdema, for large quantities may be excreted with comparatively slight œdema, as, for example, in uncomplicated amyloid disease of the kidney. Furthermore, a reduction of the albumin in the blood cannot be the sole cause of the œdema, for we know that with plenty of food there is no diminution of albumin in these cases. When cachexia develops, the albumin may, indeed, be diminished and œdema may appear, but this is of a different character and of relatively slight degree.

It is possible that the œdema of nephritis is produced by a primary retention of water in the body. In the forms of the disease under consideration, less urine than normal is usually secreted, and frequently the œdema increases as the urine diminishes, and *vice versa*. Many writers, therefore, favor the view that a primary retention of water in the bodies of these patients dilutes their blood and so produces an hydræmia or an hydræmic plethora; and Hammerschlag[169] has shown that a diluted blood is usually present in these cases of nephritis. Nevertheless, the theory has many opponents. Most experimenters have failed to produce an œdema by the mere infusion of salt solution.[170] Half of the blood has been withdrawn and replaced by saline solution and enormous quantities of fluid have been infused without producing any œdema. Some other factor, therefore, seems to be necessary, and this is possibly an injury to the vessel wall, just as in the inflammatory type. Magnus has discovered a whole series of substances which will produce extensive anasarca if injected into an hydræmic animal. Among these are substances that are retained in the body after removal of the kidneys.

One may assume, therefore, that some change in the capillary walls is, in part, responsible for the œdema of nephritis, though up to the present these changes have not been demonstrated anatomically. We have already seen that such

hypothetical changes in the blood-vessels probably account for the cardiac hypertrophy in certain cases of nephritis. Recent experimental studies[171] devoted to this problem indicate that in the nephritides produced by certain poisons the parenchymatous changes are inadequate to explain the œdema, and that the latter is doubtless due to a functional disturbance of the renal vessels. Thus in uranium nephritis, which is essentially tubular in character, œdema does not develop until the permeability of the renal vessels and their ability to contract, and especially to dilate, are affected. This would indicate a corresponding injury of the cutaneous vessels.

Some nephritic œdemas apparently depend upon the retention of sodium chlorid in the body.[172] The normal individual excretes this salt at about the same rate as it is ingested, so that the amount in the body remains nearly constant. In nephritis, on the contrary, the excretion frequently does not follow the same curve as the ingestion. The French school, especially, has explained certain cases of nephritic œdema on the basis of a retention of chlorids in the body. According to this hypothesis the inability of the kidneys to eliminate sodium chlorid leads to a retention of this salt in the body, and this retention, in turn, necessitates an accumulation of water in the tissues in order to maintain the proper osmotic relations. Attractive as is this conception, it leaves much to be explained, for in many cases of nephritic œdema there is no evidence of salt retention.[173]

(Fischer[174] has developed the theory of an increased hydration capacity of the colloids to explain œdema. Different colloids vary considerably in their ability to take up water, a property which depends upon the reaction of the fluid in which the colloid is immersed and upon the electrolytic content of this fluid. According to Fischer, œdema is produced when acids accumulate in the tissues and thus increase the affinity of the colloids for water, granting, of course, that the supply of the latter is adequate. The excess of acids represents either an increased metabolic production, or a faulty removal of acids formed in normal amount. In accordance with this conception œdema is to be combated by the use of substances which diminish the affinity of the colloids for water, namely, salts (electrolytes). Fischer has recommended definite saline solutions and a definite technic for the employment of these in cases of œdema.—Ed.)

Other Œdemas.—We know little concerning the dropsies caused by severe cachexias and by many diseases of the cord and of the peripheral nerves. Changes in the composition of the blood probably contribute to the causation of the former, while, in the latter, paralyses of the muscles would interfere with the movements of the lymph and so tend to produce œdema. Yet in neither case do these seem to be the sole causes.

Composition of Exudates.—The composition of exudates varies with their origin.[175] Those due to inflammatory causes usually contain four per cent. of albumin or over, while those due to other causes, usually contain between 0.1 and 0.8 per cent. The exudates that are poorest in albumin are those caused by cachexias and by chronic nephritides, a percentage less than 0.1 rarely being found except in serious renal diseases, especially in amyloid disease of the kidney. The percentages of albumin in exudates of a non-inflammatory character vary so much in the individual cases that a classification according to this standard is not possible. (Of considerably greater moment as a diagnostic standard is the differential count of the white cells found in the exudate (**cytodiagnosis**). Three typical formulas are described, according to the variety of cells found in greatest abundance—first, the lymphocytic, in tuberculous inflammations; second, the polynuclear leucocytic in non-tuberculous infections; and third, the endothelial in transudations. These formulas appear to be fairly specific for the different types of most exudates except the ascitic.—Ed.)

Chylous and Chyliform Ascites.[176]—Exudates into the peritoneal cavity, and more rarely those into the pericardial and pleural cavities, may contain considerable amounts of fat. This may arise from a fatty degeneration of the cells of the exudate, with subsequent disintegration of these cells. When the blood contains large quantities of fat, the latter sometimes passes through the capillary walls into the exudate. Such exudates into the peritoneal cavity are called chyliform ascites.

In another group of cases, usually caused by carcinomata, the abdominal lymphatics rupture and the chyle flows directly into the peritoneal cavity, producing the so-called true chylous ascites. The composition of the ascitic fluid then depends largely upon the character of the food, and when certain fats are ingested, they may be demonstrated in the ascitic fluid. Dur-

ing life it is often impossible to differentiate these two forms of ascites.

Pulmonary Œdema.—Œdema of the lungs may result from the same causes as does œdema of other parts of the body. The exudation about an inflammatory area corresponds to the inflammatory œdema already described (p. 91). On account of the rich and peculiar blood-supply of the lungs, however, a local œdema from stasis does not occur. If there be a hindrance to the blood-flow through one part of the lungs, the blood merely takes another course. No sharp line can be drawn between local inflammatory œdema of the lungs and a small pneumonic patch.

Of great interest is the cause of the general pulmonary œdema that so frequently terminates cardiac, pulmonary and infectious diseases. Two hypotheses have been advanced in explanation of this œdema. The first considers that it is caused by stasis. If, experimentally, the left ventricle of an animal be seriously injured while the right is left intact, pulmonary œdema frequently develops. The œdema in such instances is evidently caused by stasis, and we have reason to believe that at least some pulmonary œdemas of man are similarly produced. This, in all probability, is the cause of the œdema that sometimes develops after sudden, severe injury to the left heart, such as may be produced, for example, by an aortic insufficiency.

In order to produce this œdema experimentally, it is necessary that the left ventricle should be almost completely paralyzed; for if it be only relatively weakened, no œdema of the lungs ensues.[177] Now the general arterial pressure of patients with pulmonary œdema, especially when the latter follows nephritis or arteriosclerosis, rarely reaches the low level that is experimentally necessary, and in these patients, there is certainly no complete paralysis of the left ventricle. Sahli, therefore, believes that general pulmonary œdema results in most instances from changes in the capillary walls.[178] A number of facts support this view. First, the œdema is unevenly distributed throughout the lungs; and secondly, it is often associated with definite inflammatory processes. Indeed, in heart disease, often no sharp line can be drawn between the œdematous areas and the pneumonic patches that are so frequently encountered. Some œdemas of the lungs are, therefore, almost certainly of an inflammatory nature. Pos-

sibly future observations on the percentage of albumin in the œdematous fluid will give some indication as to the nature of its cause.

Though it must be acknowledged that inflammatory processes do contribute to the production of certain pulmonary œdemas, nevertheless it seems to me that the weakness of the left ventricle is, at least, of equal importance in most cases. The results of animal experimentation are not directly applicable to man. The chronic pulmonary stasis that accompanies heart and kidney diseases may induce changes in the walls of the capillaries of the lung, so that a relatively slight weakness of the left ventricle could produce œdema, which would not be the case if the vessels were entirely healthy. Not infrequently, the physician sees patients in whom a weakening of the left ventricle is followed by an œdema of the lungs, which disappears with a strengthening of the ventricle.

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CHAPTER II

THE BLOOD

General Considerations.—The pathology of the blood[1] is intimately associated with that of every individual organ in the body, for it is the connecting link between all of them, receiving material from and giving material to each. Its constitution depends, therefore, to a great extent upon the functional condition of the different organs. It contains a great variety of substances; yet the rapidity of the blood-current, the minute quantities of many of these present, and the rapid excretion of those which are present in excess allow the blood to maintain a fairly constant composition.

It is incorrect, therefore, to designate any particular tissue as the blood-forming organ. Every tissue in the body furnishes its contribution to the blood, and when an organ is spoken of as a blood-forming organ it is usually implied that it gives to the blood some of its more striking elements, the blood-corpuscles.

Obviously then, the composition of the blood will change whenever there are pathological changes in the activity of any organ that furnishes metabolic products to the circulation.[2] Viewed from this basis, there is a great number of blood diseases, among them diabetes and the majority of hepatic and renal disorders. Clinically, however, it is customary to speak of diseases of the blood only when the changes in the blood dominate the pathological picture, or when the cause of the blood changes is unknown. As our knowledge of these conditions increases, we shall probably find that the number of cases in which the blood changes are really primary, the so-called diseases of the blood, is exceedingly small, if, indeed, all such cases are not secondary to disease elsewhere.[3]

Changes in the blood-cells and in the hæmoglobin are recognized with comparative ease and for this reason are better known than are alterations in the composition of the plasma.

Anæmia

Although the term anæmia is used to designate those conditions in which the hæmoglobin or the red blood-corpuscles, or

both, are reduced, it should not be assumed that these are the only changes of consequence in anæmic blood. Alterations of perhaps equal importance take place in other constituents, and a proper understanding of anæmia will be possible only when we shall have become acquainted with all these various changes. For example, the integrity of the red corpuscles is intimately dependent upon the molecular concentration of the plasma;[4] if they be placed in solutions which contain either too large or too small a quantity of salts they become either shrunken or swollen, and in either case they may lose their hæmoglobin. The proteids of the plasma also seem to have some influence upon the property of the red cells to retain their hæmoglobin; and the presence of certain poisons in the blood will, undoubtedly, cause the escape of the hæmoglobin from the stromata of the corpuscles.

Anæmia from Hemorrhage.—Anæmia in its simplest form is due to an acute hemorrhage. If the loss of blood exceed a certain limit—which is about fifty per cent. of the total quantity—the amount left in the vessels is insufficient for the maintenance of the circulation, and the patient dies with all the symptoms of acute asphyxia, owing to the insufficient supply of blood to the tissues and especially to certain parts of the brain. This subject of acute asphyxia will be discussed in the chapter on respiration.

If the hemorrhage does not exceed this limit, the fluid portion of the blood lost is rapidly replaced by fluids from the tissues and food. The proteids and the corpuscles are replaced more gradually by an increased functional activity on the part of the tissues which furnish them; and finally, after weeks, or perhaps months, the blood regains its normal composition. During the first few hours after a hemorrhage, therefore, the blood as a whole is reduced in quantity. Then follows a dilution of that present with lymph; and after this there comes the regeneration of the red corpuscles. The newly-formed corpuscles are often smaller than normal, but some may be very large and a few of them may contain nuclei. For a considerable period after the hemorrhage, the individual corpuscles contain less hæmoglobin than do normal ones, for this pigment is regenerated slowly as compared with the erythrocytes,[5] and for some time, therefore, the proportion between the percentage of hæmoglobin and the number of red corpuscles remains less than the normal. The leucocytes in the peripheral blood are usually increased in number for a short

period after the hemorrhage. The rapidity with which the blood is regenerated depends upon the amount of blood lost, upon the general nutrition of the patient and upon the treatment which he receives.

General Considerations Relative to the Chronic Anæmias.— In the chronic anæmias the blood does not return so quickly to the normal, because the cause of the anæmia remains operative. This cause may injure either the blood-forming organs or the blood-corpuscles already free in the circulation. It is well known that the blood of one animal may destroy the corpuscles of another, and we must admit the possibility that similar toxic substances may develop in the body under pathological conditions. Indeed, there is evidence that this does occur in certain diseases. Various poisons such as chloroform and potassium chlorate exert a similar injurious action upon the red blood-cells. It is also possible that an anæmia may be produced by an acceleration of the normal destruction of the red blood-cells, which becomes so rapid that the regenerative processes cannot keep pace with it. Practically the same condition is produced when repeated, small hemorrhages take place, for here again the loss of blood may be so great that the normal regenerative processes cannot supply the deficiency. This is illustrated by the anæmia of miners, due to the ankylostoma duodenale.

On the other hand, the anæmia may arise, not from an excessive loss or destruction, but from an insufficient formation of red blood-corpuscles, and it is often extremely difficult in the individual case to determine which of the two is primary. An increase in the amount of iron deposited in the liver would indicate an abnormal destruction of red corpuscles.[6] This organ normally contains a small amount of iron, but in anæmia the amount is often greatly increased; and not infrequently the spleen, kidneys and bone-marrow also show abnormal deposits of iron salts. In the anæmias that are caused not by destruction but by losses of blood through hemorrhage, such deposits do not occur; and, indeed, the iron normally present in the tissues may be reduced, for it is utilized in the formation of new corpuscles. An increased excretion of pigments derived from the hæmoglobin, *viz.*, bilirubin and uro-

bilin, is also to a certain extent indicative of an increased destruction of the erythrocytes.

The red blood-corpuscles themselves frequently undergo changes in anæmia. In the first place, they may be of irregular shape, so that hardly any two look alike (poikilocytosis). Then they may vary greatly in size (anisocytosis), some being extremely small, the so-called microcytes, while others are extremely large, the so-called macrocytes. Finally, they may show clear spaces in their protoplasm (endoglobular degenerations). All of these changes are of a degenerative character.

Peculiarities of the red cells in the stained preparation are of more uncertain significance. The normal mature erythrocyte is acidophile, the stain being even, though somewhat more intense toward the periphery. Youthful types, on the contrary, take both the basic and the acid stains (polychromatophilia).[7] Two facts speak distinctly for the view that polychromatophilia is an evidence of immaturity. In the first place, this anomalous staining is shown by cells still in the bone-marrow, which are definitely immature because they contain nuclei; and further, in the circulating blood, polychromatic erythrocytes are often seen with nuclei in active mitosis. Polychromatophilia disappears as the cell ripens, though it may return coincidently with the recurrence of certain injurious influences. On the other hand, this staining peculiarity is seen also in cells undergoing disintegration outside the blood-vessels, in which case the multi-tints are diffuse, or collected where the nuclear remnants appear to be, or scattered as granules through the stroma.[8] The latter, known as granular basophilia, is particularly well marked in the anæmia of chronic lead poisoning. The old strife as to whether polychromatophilia is a sign of regeneration or of degeneration seems to have given way to the view that it may indicate either. In the circulating blood, however, the phenomenon is generally an index of immaturity.

Another evidence of regenerative processes is the presence of nucleated red cells in the circulation. Normally, nucleation is restricted to the tissues in which erythrocytes are produced, *viz.*, the red marrow of the bones, and during fetal life, the liver and spleen.[9] The red cells that pass into the blood, normally, have already lost their nuclei. In conditions of active regenera-

tion, however, such as are observed after severe hemorrhage, nucleated red blood-corpuscles appear in the blood, released in all probability before maturity. In the more severe grades of anæmia, we encounter, in addition to the nucleated cells of normal size (normoblasts), abnormally large examples (megaloblasts, gigantoblasts). The presence of the latter is considered by some to indicate that regeneration has assumed a pathological trend; in other words, that there has been a return to the embryonic state. For reasons which will appear in the discussion of pernicious anæmia, we prefer to regard these cells merely as the products of an extremely stormy regeneration of red corpuscles, and not as pathognomonic of pernicious anæmia alone. If the demand for new cells is especially urgent, the normal resources prove inadequate and the blood-forming tissues active in fetal life are again called upon. To this extent only is the megaloblast a specific type or an evolutional product of the embryonal red cells.[10]

The red bone-marrow is increased in quantity in many forms of anæmia. Normally, this tissue is limited to the flat bones and to the extremities of the long bones. If, however, the necessity arises for a greater production of red cells, the red marrow spreads over many bones, the change being in the nature of a compensatory process.[11] We are among those who believe that all increases of red marrow are of this nature, and that there is no necessity for making a division between normal and pathological red marrow.

Chlorosis.—Certain forms of chronic anæmia are sufficiently well defined to be distinguished clinically. Of these, we shall first consider chlorosis.[12] This occurs usually, perhaps exclusively,[13] in girls at about the time of puberty. Its cause is not well understood. Poor hygienic conditions are certainly not the sole determining factor, for the disease occurs with about equal frequency among the upper as well as the lower classes. Some have ascribed chlorosis to disturbances of the nervous system, others to diseases of the female genitalia, but to both, it seems to me, without sufficient evidence. As the only predisposing factors are those of age and sex, it is not impossible that the ovaries play a rôle, especially in susceptible individuals (v. Noorden).

The color of the skin in chlorosis usually varies from a slight

pallor to the typical, pale, greenish tint. The face, however, may be of an unusually brilliant color (chlorosis rubra). At times the patient is emaciated, though more frequently the fat is well preserved. Nervous manifestations are usually prominent.

The blood always shows a diminution in the quantity of hæmoglobin to the unit-volume, and the individual red corpuscles are usually paler than normal. Many of them are of small size, and some are deformed. In severe cases, nucleated red corpuscles may be present, either of normal size or very exceptionally of the megaloblastic type. In some cases, the number of red corpuscles is normal,[14] but usually it is moderately diminished. Limbeck[15] states that of two hundred and seventy-nine cases of chlorosis, only one hundred and five, or thirty-seven per cent., showed no diminution in the number of the red corpuscles.

That the amount of hæmoglobin is diminished has been demonstrated by colorimetric, spectrophotometric and chemical methods. The dried blood may show 0.03 per cent. of iron instead of the normal 0.06 per cent. Nevertheless, there appear to be mild cases of chlorosis showing no blood changes of significance, despite the well-marked clinical picture, and in which iron effects a complete cure.[16] This would indicate that the blood alterations in chlorosis are merely symptomatic.

As in other anæmias, the volume of the red cells is also changed. The leucocytes do not vary greatly from the normal. The percentage of water in the serum is approximately normal in the milder cases, whereas in the more severe ones it is increased. The total quantity of blood in the body seems considerable. Of other changes in the serum we know little. From the fact that patients with chlorosis show a tendency to the formation of venous thrombi, it has been assumed that their blood contains larger amounts of fibrin ferment—an assumption, however, which is incorrect. Not infrequently there is a retention of water in the body of chlorotic patients, due possibly to an increase in the total blood mass.[17]

Autopsies upon patients with chlorosis are few in number, and these have shown surprisingly little that was abnormal.[18] No degenerative changes were present in the liver, heart or kidneys, and no changes in the bone-marrow of the tibiæ were found. Virchow observed a general hypoplasia of the heart and blood-

vessels, and especially a narrowing of the aorta, and these have been assumed to be causative agents in the production of the disease. This view, however, does not appear very reasonable, for it is difficult to understand how chlorosis could heal as completely as it does if this were its cause; and, furthermore, stenosis of the aorta is known to produce quite a different set of symptoms.

Although chlorosis heals spontaneously in practically every case, the healing is greatly accelerated by the administration of iron.[19] Indeed, proper food seems to be of secondary importance, for chlorosis may develop in individuals who have lived in the best of surroundings. The brilliant results achieved by the administration of iron are in themselves almost characteristic of this type of anæmia, for in no other form do we see such striking effects, save possibly in those anæmias which result from hemorrhages.

The value of the administration of iron in chlorosis lends support to the theory that the cause of the disease is an inadequate or improper formation of the red blood-corpuscles. We possess no evidence favoring the opposite possibility, *viz.*, that there is a pathological destruction of the red cells, for degenerative changes in the red corpuscles are not marked, jaundice does not occur, and the quantity of pigments in the urine and fæces is less than normal. These facts cannot be regarded as proof that there is no pathological destruction of red cells in chlorosis, but they certainly render it very improbable. Unfortunately, we possess no evidence on the more decisive question as to whether or not there is an excessive deposit of iron pigment in the liver. Nevertheless, from the facts in our possession, we may assume that the underlying cause of chlorosis is an insufficient formation of red blood-corpuscles.

The exact manner in which iron exerts a favorable effect upon chlorosis still remains unsettled. The patients suffering from this disease ordinarily show no marked digestive disturbances,[20] although some, at least, seem to absorb fats poorly. There is likewise no conclusive evidence that their absorption of iron from the intestinal tract is less than normal, though the data upon this point are not very accurate. It is difficult, therefore, to understand why the iron salts in the food, which are sufficient for all ordinary needs, are insufficient in chlorosis. It seems to me most probable that iron cures chlorosis by acting as a stimulant to the

blood-forming organs, very much as does arsenic in certain other forms of anæmia.[21] (Indeed, it has been shown that iron and arsenic in combination are more efficacious in chlorosis than is iron alone.—Ed.)

Secondary Anæmias.—The remaining forms of anæmia[22] are, for the most part, merely symptomatic of other pathological conditions. When their etiology is known, they are termed secondary anæmias, in contradistinction to the so-called primary anæmias, the causes of which are unknown. This classification into primary and secondary anæmias is serviceable, but hardly final, for it seems certain that as we become better acquainted with the causation of anæmias the number of cases assigned to the primary group will progressively diminish, and the number classified as secondary anæmias will correspondingly increase. So closely may the blood pictures of the two types approach one another that it is often extremely difficult, or indeed impossible, to distinguish them. (Others, however, among them Nægeli, are strongly of the opinion that the two are readily distinguishable.—Ed.)

A great variety of causes may give rise to mild and moderately severe forms of secondary anæmia. Of these, we may first mention repeated hemorrhages, such as may occur from ulcer or carcinoma of the stomach, from intestinal ulcerations, from hemorrhoids, from uterine myomata, etc. Secondary anæmias may result, furthermore, from chronic poisoning, as by lead or mercury, from gastro-intestinal disease, from malignant tumors, from infections such as tuberculosis, syphilis and malaria, and from chronic diseases of the liver, kidneys, heart or nervous system. It should be remembered, however, that none of these diseases necessarily gives rise to an anæmia, which is the result probably of some special moment.

It is still uncertain in what manner many of these diseases produce the anæmia. Infectious processes frequently injure the red blood-corpuscles directly, as may be inferred from the degeneration which they produce in these cells. Yet the destruction of a few corpuscles, more or less, would hardly give rise to an anæmia, for the loss of a considerable number would immediately be balanced by regenerative processes. In malaria, the plasmodia

certainly destroy the corpuscles in large numbers, and this seems to be the direct cause of the malarial cachexia. In nephritis, the reduction in the number of red cells per unit of volume may be due in part to a dilution of the blood, and in part, as in hemorrhagic nephritis, to repeated losses of blood in the urine. An injury to the blood-forming tissues is a possible explanation that must not be lost sight of.

Insufficient nourishment will give rise to an anæmia in some cases. An absolute fast, even if continued up to death, merely causes a reduction in the total quantity of blood with no diminution in the hæmoglobin or red corpuscles to the unit of volume.[23] If, after such a fast, food and liquids be taken in sufficient quantity, water is rapidly added to the blood, with a resulting reduction in the percentage of hæmoglobin and in the number of red cells per unit-volume. The prolonged use of food, deficient in some important constituent, will also cause an anæmia. For example, a continuous milk diet will have this effect, on account of the small quantity of iron in the milk. Especially injurious is the combination of improper food and continued hard work. Other favoring factors are care and worry, poor light, poor air, lack of sleep, etc. Patients with anæmia from such causes exhibit a striking improvement if their surroundings are bettered, and although their absorption of iron may be less than normal, yet the simple administration of salts of this metal, without a change in their surroundings, has comparatively little effect upon their anæmia.[24]

On the other hand, mild and moderately severe secondary anæmias of this character may occur in patients who live under the best of hygienic surroundings, in which case we are unable to form any conception as to their cause. Many such individuals seem to feel perfectly well, so that one might almost question whether their anæmia was physiological or pathological. Others, however, suffer from the same symptoms as do most anæmic patients, these symptoms being especially marked upon exertion.

The blood picture in the secondary anæmias may show considerable variations. In some patients the changes are hardly demonstrable, while in others they may be of the most extreme grade.

Certain possible fallacies in the methods of blood examination should be noted. In the first place, the ordinary examination

of the blood may show nothing abnormal, and yet there may be a reduction or an increase in the total quantity of blood in the body. On the other hand, it is possible that the blood may be of different constitution in different parts of the body, so that the cutaneous capillaries contain relatively few or relatively many corpuscles.[25] Such possibilities of error cannot be easily eliminated in our clinical methods of blood examination.

In secondary anæmia the red cells frequently vary in staining properties (polychromatophilia) and in shape (poikilocytosis). The dimensions of the cells may vary more widely than in health, so that we find microcytes and occasionally megalocytes. Signs of rapid regeneration are also frequently met with, especially nucleated red cells of normal size (normoblasts), and, very rarely, nucleated red cells of large size (megaloblasts). All these changes are dependent rather upon the severity of the anæmia than upon its cause. As a rule, the white cells are normal unless some special cause for a leucocytosis is present. Changes in the blood-serum will be considered in another place.

Pernicious Anæmia.—In the third form of anæmia, the so-called pernicious form, the changes suffered by the red cells reach their maximum. Their number is greatly reduced; and Quincke has reported a case in which only one hundred and forty-three thousand per cubic millimetre were counted. The hæmoglobin is also markedly diminished, although, as a rule, it is relatively less reduced than is the number of the red corpuscles; in other words, the average red corpuscle contains as much coloring matter as the normal cell, and often indeed more (characteristic high color-index).[26] Poikilocytosis becomes extreme. At times, only a small proportion of the red cells present a normal appearance, the majority showing some one or other of the many changes which have already been described. Nucleated red cells are especially numerous—the most characteristic and often the predominating form being the megaloblast. The nuclei of these cells are often found in the process of division. The leucocytes are only rarely increased; usually their number is normal or is diminished. (These changes are subject to great variations depending upon the activity or exhaustion of the bone-marrow.—Ed.)

As a rule, in pernicious anæmia, the blood serum is not particularly deficient in solids. Grawitz[27] found, however, that

such a deficit is apt to be marked in those cases of severe anæmia which are due to malignant tumors or to chronic infectious diseases. Indeed, he has shown experimentally that pieces of carcinoma introduced into the circulation of animals will attract lymph and thereby cause a dilution of the blood-plasma. The weight of the total solids of the blood is always markedly diminished [28] owing to the small number of corpuscles. The total amount of blood in the body also appears to be less than normal, if we may judge from the impressions received at the bedside and at autopsy.

The effects of a very severe anæmia upon the patient are often most striking. His brain and muscles are easily fatigued, he suffers from shortness of breath and from fainting spells, and gastric secretion is diminished or entirely absent. There is often a great tendency to bleeding, especially into the skin and retinæ. Fatty degeneration of various organs is the rule, being especially marked in the liver, the kidneys and above all in the heart-muscle. Not infrequently, fever is present, due possibly to substances liberated from the disintegrated red blood-corpuscles, though as to this explanation there is still some uncertainty.

Very remarkable changes are found in the central nervous system in pernicious anæmia.[29] The most frequent anatomical lesion is degeneration of the posterior columns of the spinal cord, though the lateral columns and the gray matter may also be diseased. The cause of these changes is still uncertain. Some believe that they are caused by hemorrhages, others that they are due independently to toxic influences.

The pernicious form of anæmia must be regarded merely as a symptom-complex which may be caused by a variety of pathological processes. For a certain group of cases no cause has yet been found,[30] and to these is given the name of essential pernicious anæmia, or the Biermer-Addison type of anæmia.[31] Such cases appear to be especially frequent in certain localities, *e.g.*, Switzerland.

The blood-picture which we have described was at one time regarded as characteristic of this essential pernicious anæmia of unknown causation; yet time has shown that the same blood-findings may be present in anæmias of

known origin.[32] There has been a continual endeavor on the part of certain investigators to differentiate these two forms of pernicious anæmia, and special emphasis has been laid upon the presence of megaloblasts as favoring the diagnosis of the essential pernicious form. Yet megaloblasts have also been found in the secondary form of pernicious anæmia. Among the diseases which have given rise to a pernicious type of anæmia are syphilis, carcinoma of the stomach, gastric ulcer, ulcerating carcinoma of the uterus, hepatic affections and diseases of the bone-marrow. Hunter has stated that the condition may be produced by a chronic intoxication from oral sepsis, yet this view has not received general acceptance. It has also been asserted that pernicious anæmia is caused by toxins of intestinal origin. Atrophy of the gastro-intestinal mucous membrane is frequently present in pernicious anæmia, but we know that it may also occur without causing the disease. Some believe that repeated small hemorrhages may be a causative factor, although this is denied by others. It is universally agreed, however, that at least two forms of intestinal parasites, bothriocephalus latus and ankylostoma duodenale, may produce a pernicious type of anæmia. From these numerous observations it has been proved that it is impossible to draw any sharp distinguishing line between those anæmias of a pernicious type that are due to known causes, and those that appear to be primary.

Our views on pernicious anæmia will hardly meet with general approval. That the term "pernicious" is applicable only to the essential Biermer type and to bothriocephalus anæmia is universally agreed. But no less authoritative a hæmatologist than Nægeli denies that the anæmia of gastric carcinoma and of ankylostomiasis is of this type. The effort is constant to find in the blood changes that will distinguish the pernicious from the non-pernicious forms. The presence of megaloblasts was at first regarded as a distinctive criterion, while now the high color-index is emphasized. According to Nægeli, an index over one does not occur in cancer of the stomach; in this, however, Pappenheim does not concur. In our opinion, a high index is merely a sign of great regeneration,

such as occurs in embryonic blood.[33] Too great importance, therefore, must not be attached to details of this kind, and especially must the blood changes not be over-emphasized at the expense of changes in other organs. Only a better understanding of the etiological factors will enable us to write the last word on these anæmias.

In what manner the various causes affect the blood is not always clear. With the possible exception of the ankylostoma duodenale, it seems improbable that losses of blood play any great rôle. In the case of malignant tumors, hæmolytic toxins are possibly responsible for the blood condition. It seems very probable also that this is the case in the anæmia produced by the bothriocephalus latus.[34] Recent studies have attached great importance to the action of a lipoid substance in the causation of bothriocephalus anæmia and of hæmolytic conditions generally.[35] Apparently, many individuals harboring intestinal parasites become immunized against their poisons, a supposition which would explain the fact that a man may have the parasites in his intestines without manifesting any symptoms, and that periods of improvement and relapse may alternate.

The prognosis of the pernicious form of anæmia depends mainly upon its cause. In the primary, essential form, the outcome is usually fatal; in the secondary forms, recovery may take place if the cause be discovered and removed, and if the process be not already too far advanced. This is especially true of those cases due to intestinal parasites.

In pernicious anæmia there is unquestionably an increased destruction of the red blood-corpuscles, as is proved especially by the abnormal deposits of iron salts in the liver and in other organs. This destruction, further, is probably of toxic origin, for the anæmias caused by losses of blood or of serum, even though most severe, are unaccompanied by such deposits of iron. The pigmentation so frequently found in the spleen, the bone-marrow, the kidneys and the liver, the not infrequent jaundice,[36] the increase in the coloring matter of the urine, and the recently reported hæmoglobinæmia likewise support the idea that in pernicious anæmia there is an unusual destruction of the red blood-corpuscles.

On the other hand, we have evidence that there is also

an increased regeneration of erythrocytes, for the red bone-marrow spreads to parts of the bones from which it is normally absent, and in this red marrow are found erythrocytes of various kinds, but more particularly the large nucleated variety known as megaloblasts. By the escape of these cells into the blood, one of the most characteristic features of pernicious anæmia is produced. And, furthermore, there is a return to embryonic conditions in that certain organs, particularly the liver and spleen, once more take on a blood-building function, evidenced by the myeloid metaplasia.

In pernicious anæmia, therefore, there is both an increased destruction and an increased regeneration of red corpuscles, but we do not know at present which process is primarily at fault. Perhaps the destruction of the erythrocytes is so intense that even the most marked regeneration does not replace the cells destroyed; or perhaps the new cells are so imperfect that they cannot resist the normal wear and tear in the body, and consequently disintegrate with abnormal ease. Some hold that the disease consists essentially in a return to the embryonal type of blood formation. Yet there is no reason to consider that the blood and marrow changes are other than would result from an excessively active regeneration of erythrocytes, with the escape of immature corpuscles into the circulating blood. We do, however, possess direct evidence that the red corpuscles of pernicious anæmia are more vulnerable to injury than the normal corpuscles, and that they may be destroyed with comparative ease. This seems to be especially true of the malignant anæmia of syphilis. (A considerable literature[37] has appeared in the past few years relative to the removal of the spleen in cases of pernicious anæmia. The indication for the operation cannot be drawn along the same lines as that for hæmolytic jaundice, because pernicious anæmia, as a rule, exhibits no fragility of the red blood-cells, but rather an increased resistance to hypotonic salt solutions (Türk). Observers are by no means in accord as to the cases appropriate for operation, nor as to the evidence of improvement following splenectomy.—Ed.)

In addition to the Biermer type of pernicious anæmia, there is one in which the regeneration of erythrocytes seems to be particularly at fault. This is the so-called aplastic anæmia.[38] The blood-picture is not especially characteristic, aside from the

complete absence of all forms of nucleated red corpuscles. The prognosis of the aplastic anæmias is no less grave than that in the usual form. At autopsy, the bone-marrow appears excessively poor in erythroblasts and sometimes also in leucocytes. Infections of different sorts, malaria for example, are possible causative factors in some of these anæmias.[39] Animals subjected to repeated venesection, and at the same time receiving insufficient food, may show a similar bone-marrow.[40]

It must be emphasized, incidentally, that in severe anæmias especially, the blood-picture is by no means an infallible index of conditions in the blood-building organs. Megaloblast formation in the bone-marrow may be marked without the appearance of a single one of these cells in the circulation. A certain reserve, therefore, is indicated in the diagnosis of aplastic anæmia.

Hæmoglobinæmia.—Thus far we have considered the hæmoglobin only as it constitutes a part of the red blood-corpuscles. If it escapes from the latter into the plasma, the condition is known as hæmoglobinæmia.[41] Hæmoglobin which has become free in the plasma is quickly removed, principally by the liver, and, to a lesser extent, by the spleen and the bone-marrow. If these organs fail to remove it completely, it is excreted in the urine, giving rise to hæmoglobinuria. According to Ponfick, the latter is produced when about one-sixtieth of the total hæmoglobin of the blood is set free from the cells. The stromata of the cells which have lost their hæmoglobin are deposited in the spleen, and cause a swelling of that organ. Since the liver manufactures bile-pigments from hæmoglobin, the bile becomes unusually rich in coloring matter and the fæces become darker. The hæmoglobin which is removed by the liver and kidneys is naturally lost to the body, but even that which remains dissolved in the plasma is in part rendered useless as an oxygen-carrier by being transformed into methæmoglobin, a compound isomeric with oxyhæmoglobin, but differing from it, in that it is unable to give up its oxygen in the tissues.

Such a passage of the hæmoglobin from the corpuscles into the plasma, or, as it is called, hæmolysis, may be brought about by several causes. The osmotic tension of the red cells may be so increased that they become unable to retain their hæmoglobin; or, on the other hand, a

lowering of the osmotic pressure of the plasma may bring about the same result. The latter seems to be of comparatively little importance, for normal red cells are resistant to considerable changes in the osmotic pressure of the plasma, and large amounts of water may be infused into the circulation without causing a laking of the blood. Of far greater importance as a cause of laking are chemical changes in the corpuscular stromata and envelopes, which are composed largely of fat-like substances.[42]

We have said that the hæmoglobin free in the plasma may become converted in part into methæmoglobin. Certain poisons possess the property of effecting this conversion of the hæmoglobin directly within the red cells. If the injury to these cells be not too severe, it is possible that the methæmoglobin so produced may be transformed again into oxyhæmoglobin. If the corpuscles are more seriously damaged, however, they disintegrate and their coloring-matter passes into solution.

Three different processes may, therefore, give rise to hæmoglobinæmia: first, osmotic changes in the plasma; secondly, a primary injury to the red blood-corpuscles; and thirdly, a primary transformation of the oxyhæmoglobin into methæmoglobin. These processes may run courses quite independent of each other, but for the most part they are combined, to some extent, and it is often difficult, in the individual case, to say which was really the primary change.

Of the poisons[43] which will give rise to a laking of the blood, we may name those of the poisonous fungi, the bile salts, arseniuretted hydrogen and the plasma of alien animals. The toxins produced by microorganisms may also injure the corpuscles; and hæmoglobinæmia has been observed in severe cases of typhoid fever, scarlet fever and other infectious processes, being especially severe in certain forms of tropical malaria (black-water fever). In such cases the plasma dissolves its own corpuscles. Italian observers have described such a globulicidal action of the plasma in association with a great variety of diseases. Whenever the destruction of the corpuscles exceeds a certain limit, hæmoglobinæmia and, ultimately, hæmoglobinuria occur.

According to the recent observations[44] from Hofmeister's

laboratory, it seems probable that those substances which dissolve erythrocytes do so by dissolving or precipitating the constituents of the stromata, especially the lecithin and cholesterin.

Paroxysmal Hæmoglobinuria.—The condition known as paroxysmal hæmoglobinuria[45] is characterized by the passage of red to dark-brown urine. The latter contains some of the more usual forms of albumin, but its characteristic color is due to the presence of free oxyhæmoglobin and methæmoglobin, with few if any red blood-corpuscles in the typical cases. The paroxysm is usually accompanied by chills, fever and pains in various parts of the body. As a rule, the liver and spleen become enlarged, and, in addition, jaundice may develop. Occasionally, a sense of anxiousness, or of suffocation, is complained of. After a few hours or days, the symptoms disappear, and only the dark-colored fæces remain as evidence of the paroxysm which has just ceased. In other cases, subjective manifestations may be practically absent, or on the contrary, extremely severe.

Malaria and particularly syphilis appear to be predisposing causes of this disease. In some individuals the attack is precipitated by muscular exertion, in others by exposure to cold. Indeed, some patients void the characteristic urine whenever they are exposed to a low temperature, or even when a hand is dipped into iced water. During the intervals between the paroxysms, the patient may appear to be perfectly well, or he may continue to show albumin in the urine. Ralfe has reported the case of a man who had cyclic albuminuria in conjunction with paroxysmal hæmoglobinuria, and a similar case has been observed by the author.

The escape of the hæmoglobin is due to the action of an hæmolysin[46] of inconstant properties. In the majority of cases, it would seem that an amboceptor-like body is fixed to the red blood-cells only at low temperatures. The hæmolytic system would then be completed by complement normally present in the individual's serum. The amount of complement available, however, apparently varies greatly,[47] being especially low at the height of an attack. Such a diminution would be compensatory in nature, as it would halt further hæmolysis and thus end the paroxysm; while in the intervals

between attacks, it is likely that the hæmolytic amboceptor is greatly reduced or even absent.

There is no evidence to show that the red cells themselves have suffered an injury in paroxysmal hæmoglobinuria; nevertheless they are generally credited with harboring the noxious factor, because the serum does not contain it. As a matter of fact, the red corpuscles sometimes appear to have an abnormally low resistance, though the significance of this is not clear.[48] Possibly variations in the partial pressure of carbon dioxide in the blood play a part in the hæmolytic process.

The hæmoglobinuria is generally accompanied by a hæmoglobinæmia, though cases are on record in which the plasma contained no coloring matter. It is by no means impossible, therefore, that complement first becomes active in the kidneys. The position of syphilis in this condition presents an interesting problem, namely, that of a possible relationship between the hæmolysin concerned in the Wassermann reaction and the hæmolytic amboceptor active in hæmoglobinuria.

The periodic attacks in the condition under discussion bear a close resemblance clinically to those following transfusion with an alien blood. It is reasonable to assume, therefore, that both are of similar origin, this being an intoxication with substances derived from the erythrocytes—in one case the individual's own corpuscles, and, in the other, cells of a foreign blood. It is of practical importance, however, to remember that the blood particularly of anæmic individuals may contain isolysins,[49] so that the transfusion even of human blood may not be entirely free from danger. On the other hand, it is possible that severe hæmolytic paroxysms lead to improvement or complete recovery in anæmic conditions by stimulating the bone-marrow.

Other Causes Which Injure the Red Blood-Corpuscles.—Extensive superficial burns may cause the red corpuscles to break up into smaller particles,[50] and lead to a liberation of hæmoglobin in the plasma, not only from these disintegrated corpuscles but from others, which, microscopically at least, appear to be normal. The oxyhæmoglobin, dissolved in the plasma, is taken up by the liver and kidneys, partly as methæmoglobin, the urine consequently containing both these pigments. The cellular residues are taken up especially by the spleen and

bone-marrow, and, to a lesser extent, by other organs. The symptoms they produce will be described later.

Many poisons are able to convert the hæmoglobin of the red blood-corpuscles into methæmoglobin,[51] among the more important of which are potassium chlorate, acetanilid and other coal-tar products. The first does not exert the same action upon the blood of all species of animals, the corpuscles of some appearing to be especially resistant to its action. Even in the same individual, accessory factors may render the corpuscles more or less vulnerable to the action of potassium chlorate. Thus, Mering has shown that the red cells are rendered susceptible by fever or by a reduction in the normal alkalinity of the blood, produced by the administration of mineral acids. The toxic effects of the administration of potassium chlorate appear, therefore, to depend upon two factors—first, upon the amount of the salt in the blood at a given time, and secondly, upon the resistance possessed by the red corpuscles.

Systemic Effects Resulting from the Rapid Destruction of Red Blood-Corpuscles.—The effects of such a rapid disintegration of red cells upon the body as a whole depend partly upon the loss of functioning hæmoglobin and partly upon the toxic substances derived from the destroyed corpuscles. In very severe intoxications with potassium chlorate, death results from the diminution in the respiratory capacity of the blood, caused by the loss of hæmoglobin.[52]

The destruction of a large number of red corpuscles sets free in the plasma certain substances, apparently enzymes, which tend to produce intravascular clotting. A limited quantity of such substances may be neutralized or destroyed by the living organism; but when they appear in very large amounts, they give rise to thrombi in the smaller blood-vessels.[53] As results of such thrombi, necroses occur in various tissues; and the gravity of the intoxication often depends upon the localities in which the coagula form.

The fact that there is a slow coagulation of the blood in certain cases of extensive burns in no way excludes the possibility that thrombi have formed, for we know that the presence of substances in the blood which favor coagulation may in turn give rise to substances having the very opposite effect, so that ultimately coagulation will be retarded. Opinions differ as to the rôle

played by these thrombi in states of rapid blood destruction. Some observers have found them in the majority of cases, while others have missed them with equal frequency.[54]

The large quantities of hæmoglobin or methæmoglobin which may pass into the urine in these conditions seem to injure the kidneys directly, and not infrequently the urine contains large amounts of albumin, numerous blood and epithelial cells, and a great variety of casts, the most characteristic of which are composed of clumps of blood-pigment. The quantity of urine may diminish up to complete anuria, and the patient may die of uræmia. Anatomically, the uriniferous tubules are found to be blocked with masses of pigment, and in addition the epithelium itself seems to be injured. It is quite possible that some of these changes are due to the products of destruction of the stromata, but this is not certain.[55]

The White Blood-Corpuscles

The white blood-corpuscles[56] may be divided into groups according to their size, the character of their nuclei and the staining reactions of their protoplasm. About seventy per cent. are made up of cells that are slightly larger than red corpuscles, and that contain irregular nuclei and protoplasmic granules staining with neutral anilin stains (polymorphonuclear neutrophiles). From twenty-five to twenty-eight per cent. are made up of mononuclear cells, from two to four per cent. of which are quite large (large mononuclears and transitional cells), while the remainder are about the size of red blood-corpuscles (lymphocytes). In addition to these cells, there are from one to four per cent. of eosinophiles, characterized by the presence of large acid-staining granules in their protoplasm, and from one-half to two per cent. of cells containing large irregular basic granules (the mast-cells). In infants and young children, the lymphocytes are relatively more numerous and they may even exceed the neutrophilic polymorphonuclears.

Arneth,[57] more recently, has further subdivided the polynuclear leucocytes on the basis of the shape, number and size of their nuclear subdivisions, and has studied the variations in these particulars in different infections. His views rest upon the assumption that the immature polynuclears possess a nucleus

which is almost round, whereas more mature cells exhibit a number of more or less distinct nuclear parts. From this general aspect, Arneth's view may be subscribed to. Further study, however, is needed to substantiate the rather far-reaching deductions as to degeneration and regeneration, diagnosis, prognosis and treatment, etc., which some observers see fit to draw on the strength of Arneth's work. More recent writings,[58] indeed, have vigorously questioned the full scope of Arneth's interpretation. Nevertheless, a definitive judgment as to the value of the method is not justifiable at this time. (Nægeli, in the second edition of his book, summarizes the present status of the question and points out that there remains little of the original structure of the Arneth theory.—Ed.)

Little is known of the chemistry of the different types of white cells. Minkowski has found the same nucleinic acids in all white cells, though combined with different substances in the various types. Pus-cells, as well as bone-marrow elements, and the ordinary polynuclear leucocytes of the blood, are able to oxidize certain substances[59] such as the acid in guaiac resin, by means of an enzyme-like body, or oxydase, which they contain—a property not possessed by the mononuclear cells originating in the thymus, spleen and lymph-nodes. Still other oxydase reactions are shown by cells of the myeloid system, and not by those of the lymphoid. The recently described indophenol reaction[60] of Winkler and Schultz is of this character. (The oxydase reactions have found a considerable application in the differentiation of acute myeloid from acute lymphoid leukæmia, by determining, among other methods, the source—whether myeloid or lymphoid—of certain large mononuclear cells, with a non-granular cytoplasm, which occur in both forms of acute leukæmia.[61]—Ed.)

The source of the different leucocytes is still, in my opinion, an open question, and this must be settled before a classification is possible. The observer who believes that a given white blood-cell has invariable characteristics is inclined to ascribe it to a definite origin. Ehrlich has attempted such a classification, as is well known. The lymphocytes, according to him, arise only in lymphoid tissue, and the ordinary polynuclears are descendants of mononuclear bone-marrow cells. By many, however, this division is criticised because based upon too uncer-

tain and variable a standard.[62] Thus, the lymphocytes are also said to be capable of spontaneous movement. Nevertheless, in a general way, and especially in recent years, hæmatologists are inclined to accept Ehrlich's strictly genetic subdivision into lymphoid and myeloid. Nægeli and Schridde are the strongest proponents of this dualistic theory. Unlike Pappenheim and others, they do not believe in a common lymphoid mother cell in extra-uterine life, inclining rather to the view that the forerunners of the myelocytes—the myeloblasts—can be distinguished morphologically from the original lymphoid cell.

It is best, perhaps, to concede that some of these problems are still unsettled; in my opinion, they require a constant revision to prevent further research from taking a restricted bent because of pre-existing premature conclusions.

Physiological Leucocytoses.—The number of leucocytes in a cubic centimetre of blood is normally between six and eight thousand. Children have, on the average, somewhat more—about nine thousand; weak and poorly nourished persons appreciably fewer. Arneth gives as the average for the fasting healthy adult, five to six thousand. The number of leucocytes in the peripheral blood varies even in the same individual at different times. Thus it is usually increased after a meal, especially one rich in proteids.[63] Such a digestion leucocytosis is absent in some individuals normally, but it is especially apt to be absent in certain diseases, above all in carcinoma of the stomach. During pregnancy, more particularly in the later months, the number of leucocytes is increased. A leucocytosis is also physiological in the new-born. Cold baths and exercise[64] likewise increase the number of leucocytes in the peripheral blood. Some regard this latter as an effect of the more rapid blood-current, which tears the leucocytes away from the vessel walls of the internal organs and throws them into the general circulation, and especially into the peripheral capillaries from which the samples of blood are taken. Grawitz looks upon it as a genuine new formation of corpuscles.

The conditions which we have just been describing have been termed physiological leucocytoses. The increase in the number of white cells does not usually exceed thirty per cent. of the normal, although in children the number may be doubled. The proportion between the mononuclear and the polynuclear cells remains

unchanged in this form of leucocytosis. Since the counts are made from the blood of the peripheral capillaries, the question arises, Is there an actual increase in the total number of leucocytes in the blood, or is there merely a redistribution of the cells, more going to the periphery and fewer remaining in the interior of the body? Studies on animals have shown that there is normally a greater number of leucocytes at the periphery than in the internal organs, but that during the digestion leucocytosis, at least, the number in both places is increased. The new cells are probably derived from the lymph and from the various organs of the body, for no signs of an active regeneration of these cells are to be found. The digestion leucocytosis seems to be due to the presence of substances in the blood which attract the leucocytes (chemotaxis). Such substances appear to be present in largest amounts after the ingestion of proteid food, though not all varieties of proteid food exert the same influence. Indeed, it is uncertain just which products of digestion are responsible for the normal digestion leucocytosis. Possibly this leucocytosis indicates a transportation of proteid material from the intestines to other parts of the body.

A hyperleucocytosis is frequently, but not always, preceded by a hypoleucocytosis.[65] Löwit interpreted this as a primary destruction of the white corpuscles which precedes a regeneration. Goldscheider and Jacob and others, on the contrary, failed to find any sign of destruction, and believe that this hypoleucocytosis is caused by a massing of the leucocytes in the capillaries of the lungs. More work is necessary to decide this question.

Pathological Leucocytoses.—Many infections cause an increase in the number of white blood-corpuscles in the peripheral blood—the so-called pathological leucocytosis.[66] Although the same varieties of leucocytes are present as in health, the relative proportions are usually changed. In the more common forms of pathological leucocytosis, the percentage of lymphocytes is diminished, whereas that of the polymorphonuclear neutrophiles is increased—from eighty-eight to ninety-five per cent. of the latter being frequently found, as compared with the normal of seventy to eighty per cent.

In other forms of pathological leucocytosis, the relative number of the lymphocytes is increased, such a blood-picture being presented by many cases of pertussis. Of

special interest would be the investigation of the blood-changes in those diseases which give rise to exudates rich in lymphocytes, such as tuberculous meningitis and pleurisy, and certain chronic cord lesions.

The influence of the nervous system upon the number of white cells would seem to be shown by recent studies.[67] Substances like epinephrin, which stimulate the sympathetic system, produce neutrophilic leucocytoses, while those acting upon the vagus, such as pilocarpin, cause an eosinophilic leucocytosis, or a lymphocytosis. These observations, however, must be viewed conservatively.

Still another form of leucocytosis is characterized by the relative increase in the eosinophilic white blood-corpuscles. This has been observed in bronchial asthma, trichinosis and a variety of other diseases. (In most infections—scarlet fever being an exception—the eosinophiles are absent during the height of the disease. Their reappearance is regarded as a favorable sign.—Ed.)

Pathological leucocytosis of the neutrophilic type occurs especially as the result of inflammatory processes and, above all, in association with those which are accompanied by a purulent exudation, although the latter is not a necessary concomitant. In certain infectious diseases, *e.g.*, typhoid fever, malaria and uncomplicated tuberculosis, there is usually no increase in the number of white blood-corpuscles in the circulating blood.

The infectious leucocytoses are probably caused either by the secretions of the living bacteria, or by the disintegrated bodies of dead ones. Experimentally, it has been shown that various constituents of the bacterial cell may exert an attractive influence upon the leucocytes (positive chemotaxis).[68] Many other substances also appear to exert such a chemotactic influence; and the same substance may, under one set of circumstances, attract the leucocytes, and, under another, repel them. The origin of the extra leucocytes has not yet been definitely setted—we do not know whether they are derived from the bone-marrow, the lymph-glands or possibly from other tissues. The purpose of these pathological leucocytoses is probably one of resistance to the invading micro-organisms.

Leucocytoses of the neutrophilic type may also result from hemorrhage and from malignant cachexias.[69] The

latter, however, do not always cause an increase in the number of leucocytes in the peripheral blood; nor do we know what is the determining factor in the individual case. Grawitz found that after injecting carcinomatous material into an animal's blood, the latter became more dilute, and the number of leucocytes was frequently increased. These changes were believed to result from an increased flow of lymph into the blood—a possible explanation not only of the leucocytoses due to malignant disease, but of those which follow acute hemorrhage.

Leucocytoses in which the eosinophilic cells are increased occur in a variety of diseases, of which we may mention bronchial asthma, various cutaneous lesions, trichinosis[70] and infections with intestinal parasites. It is interesting that in most of these diseases there exists a local collection of eosinophilic cells at the main seat of the disease: for example, in the bronchi and in the exudate of bronchial asthma,[71] in the lesions of certain skin affections and about the embryos in trichinosis.

The number of white cells in the blood in pathological leucocytoses usually ranges between ten thousand and thirty thousand per cubic millimetre. Higher counts do occur, however, though rarely, if ever, exceeding eighty thousand.

Leucopænia.—A diminution in the number of leucocytes in the peripheral blood, a leucopænia, occurs in a variety of diseases. It has been observed in cachexias, intoxications, many anæmias and in some infectious diseases, notably in typhoid fever and malaria.

In such leucopænias, the proportion between the numbers of the various kinds of white cells is usually changed. For example, in typhoid fever there is a relative increase in the number of lymphocytes. The cause of the leucopænias is unknown. Possibly they are due to a negative chemotaxis, or to some lesion of the sites of origin of the leucocytes. In typhoid, indeed, the bone-marrow is poor in myelocytes, which would explain the relative, but not the absolute, lymphocytosis generally observed.

Little is known of pathological alterations in the **blood-platelets.**[72] It is generally agreed that these bodies are intimately associated with the phenomena of blood coagulation, in that they take a part in the formation of fibrin-ferment. In certain con-

ditions, indeed, for example, in severe anæmias, delayed clotting and a diminished number of platelets go hand in hand. The platelets contain also a ferment capable of splitting polypeptids.[73] These facts would indicate that the platelets are biological entities, and not merely disintegrated erythrocytes. Their origin is not known, nor are the variations they undergo in pathological conditions, aside from the fact that they are reduced in certain severe anæmias. (Their extreme reduction in pernicious anæmia seems to have a diagnostic value; while in chronic myeloid leukæmia they are generally enormously increased.—Ed.)

Leukæmia and Pseudoleukæmia.—(The author uses the term pseudoleukæmia, for the most part, in the strict sense, as denoting the condition in which the pathological picture, both gross and microscopic, is typically leukæmic, but in which the characteristic leukæmic changes are absent in the blood. This so-called aleukæmic leukæmia may be either lymphoid or myeloid. This strict interpretation excludes the many conditions, such as malignant granulomatosis (Hodgkin's disease), tuberculosis, syphilis, lymphosarcomatosis, etc., which clinically may bear a close resemblance to pseudoleukæmia.—Ed.)

In leukæmia and pseudoleukæmia,[74] there is obviously a conjoined disturbance of the bone-marrow, the lymphadenoid tissues and of the spleen; and, in addition, there are generally changes in the blood. It is convenient, first, to consider the two diseases together and then in their relationship to one another. The change in both consists of a hyperplasia of the spleen, lymph-nodes and bone-marrow, or only of two of these organs; in leukæmia, the bone-marrow is apparently involved in all cases.

Two types of leukæmia are recognized, depending upon the character of the cells present in the circulation and in the hæmapoietic organs. Corresponding also to the types of cells found increased in the blood, the hyperplasias in the different organs concerned in blood building—bone-marrow, spleen, lymph-nodes, liver, intestines—exhibit diverse cells (myeloid and lymphoid hyperplasia). In pseudoleukæmia, the histological changes in the above-mentioned organs generally resemble those of lymphoid leukæmia, though in some cases the myeloid type is observed.

The bone-marrow[75] of the long bones does not consist chiefly of fat cells, as in the healthy adult, but returns to its lymphoid character, such as one sees in childhood, and in the anæmias. In color it varies from a deep red to a grayish-yellow, though the findings are not uniform in all cases either of leukæmia or of pseudoleukæmia. At times, the marrow is indistinguishable, grossly and microscopically, from that seen in many anæmias. Histologically, there are observed nucleated red cells of all types, and in addition an enormous number of leucocytes. The latter, indeed, may be so numerous as to lend to the marrow a pus-like appearance. These white cells are of myeloid type in some cases, and of lymphoid in others.

In the spleen and lymph-nodes the hyperplasia, according to the general opinion, has no specific anatomical character. The growth in lymphoid leukæmia concerns the autochtonous lymphoid tissue; while in the myeloid form, there is a growth of cells of the bone-marrow type, *i.e.*, there occurs a myeloid conversion of the lymph-node.

These hyperplasias are not confined to the bone-marrow, lymph-nodes and spleen, but appear wherever there is lymphoid or myeloid tissue capable of growth. Even the cells of the vessel walls—comprising the original mother-substance—may be the source of new cells. The lymphoid and myeloid cell-accumulations occurring in the liver, spleen, intestines, thymus, skin, tonsils, choroid, etc., are partly metastatic in nature and partly metaplastic. Pappenheim, Nægeli, indeed hæmatologists generally, view this as a metaplasia *in loco* and not as a blood-cell colonization, *i.e.*, transported from elsewhere. In the lymphoid processes, the hyperplasia seems to be more widely distributed than in the myeloid.[76]

In the leukæmias there is generally a marked, often an enormous, increase in the white cells in the blood, while in pseudoleukæmia there is either no increase or at most a moderate one. According to Pinkus,[77] there is regularly a relative increase in the lymphocytes in pseudoleukæmia, and herein lies the intimate relationship between the latter and lymphoid leukæmia. Indeed, the two conditions differ only in the fact that the number of white cells in the blood is increased in the one and normal in the other. This criterion has certain limitations, however, for, as already

mentioned, pseudoleukæmias occur with a myeloid type of origin and with myeloid blood-changes (amyelæmic and submyelæmic leukæmias). We distinguish, therefore, between myeloid and lymphoid tissue hyperplasias, with or without an increase of the corresponding cells in the circulating blood.

The leukæmias may be differentiated from the leucocytoses, in a general way, by the greater increase in the white cells. In the former, values of three to five hundred thousand cells are not infrequent; at times, indeed, the white cells may be as numerous as the red. In a leucocytosis, on the contrary, a white count above eighty thousand scarcely occurs. A more important index, however, of the leukæmic nature of a process resides in the types of white cells present, for the number of cells may undergo considerable variations during the course of the disease. (A diminution, for example, may occur during an intercurrent acute infection, and also as a result of X-ray therapy.[78] The use of benzene,[79] as recommended by Korányi, has produced similar results. In these cases, however, though the total number of white cells may be reduced even to a normal level, the differential count ordinarily shows little change in the relative proportion of pathological cells present, the blood remaining typically leukæmic.—Ed.) The former tendency, therefore, of looking upon the number of white cells as the sole criterion of a leukæmia resulted in a narrow and indistinct picture of the disease, so that to-day it is difficult to interpret the earlier literature on the subject. An unequivocal diagnosis of leukæmia demands not only a careful histological scrutiny of the organs involved, but also the demonstration of certain types of white cells in the blood.

Characteristic of the leukæmias is the presence in the circulation of cells normally absent, and particularly is the relative proportion of the different forms unlike that in the leucocytoses. In the latter, the polynuclear neutrophiles preponderate; in leukæmia, on the contrary, mononuclear types are always strongly in evidence, their number varying within wide limits. In the acute leukæmias the mononuclear forms are much more numerous than in the chronic; indeed, they may comprise ninety-nine per cent. of all the white cells present.

Two types of leukæmia are distinguished according to their blood-pictures. The first exhibits

a great many large mononuclear cells with abundant, predominantly neutrophilic, granules in the cytoplasm (*myelocytes*). The polynuclear neutrophiles are absolutely increased though relatively diminished. Various atypical leucocytes are common, as are nucleated red corpuscles, usually of moderate size. (Indeed the very multiplicity of atypical forms is indicative of myeloid leukæmia.—Ed.)

Myelocytes, though absent from normal blood, are not pathognomonic of leukæmia, for they occur, less abundantly it is true, in other conditions,[80] notably in the infectious diseases, and in severe anæmias. An interesting resemblance to the blood of myeloid leukæmia is that due to tumors which have given rise to metastases in the bone-marrow.

In the second type of leukæmia (*lymphoid or lymphatic leukæmia*), the prevailing cell is the small, or moderately large, mononuclear, the so-called lymphocyte, with a large nucleus and a narrow rim of non-granular cytoplasm. The other types of white cells, in particular the polynuclear neutrophiles, are relatively and often absolutely decreased. Eosinophiles and myelocytes are usually absent, though in certain cases of lymphatic leukæmia the latter cell may be fairly numerous. The red cell count may remain unchanged for a long time, later being diminished. Nucleation is rare.

The two forms just described are readily differentiated, for the predominant cell in each points to a hyperplasia of the myeloid or lymphoid tissues, as the case may be. The type of cell found in the blood is not indicative of the organ whence it originated; whether the spleen or lymph-nodes are predominantly affected is more readily judged from the ordinary methods of physical examination.

A genuine anæmia is generally observed in leukæmia and pseudoleukæmia; both oligocythæmia and oligochromæmia are present. Poikilocytes and nucleated red cells of various sizes may be seen. In certain cases, therefore, the blood may closely resemble that of myeloid pseudoleukæmia and of the Biermer type of pernicious anæmia.[81] These are the cases of so-called **leukanæmia** (Leube), the nature of which is little understood, though the blood-changes point to a coincident injury to the erythropoietic and leukopoietic functions of the bone-marrow. (Certain observers, such as Nægeli, seriously doubt the

existence of such a leukanæmia, believing that more rigid analyses would show that conditions going under this name are in reality pernicious anæmia, myeloid leukæmia—acute or chronic—or other processes.—Ed.)

The blood-serum in leukæmia sometimes contains proteids not normally present. Nucleo-albumins and deutero-albumoses have been found, but at present the meaning of these findings is not clear. Charcot-Leyden crystals have been found in myeloid leukæmia in the blood, as well as in the fluids of the spleen. These crystals appear to bear some relation to the presence of eosinophilic cells.

Leukæmia is generally a disease of middle life, though it may occur both in children and in the aged. It terminates fatally in practically all cases: instances of recovery were not unlikely leucocytoses. The beneficial action of the X-ray[82] has recently come to the fore, thorough rœntgenization of the spleen and of the long bones often producing not only a marked decrease in the number of leucocytes, but also a decided reduction in the size of the spleen and lymph-nodes. The action of the rays seems to be exerted both upon the marrow and upon the white cells in the blood. Improvement, approaching recovery, has been observed; but this is temporary and the blood qualitatively usually remains leukæmic. The author has seen conditions aggravated by the use of the rays. (The use of benzene has already been commented upon. Its effects are generally similar to those of the X-ray; the results, indeed, seem best when the two methods are combined. The toxic action of benzene, particularly upon the kidneys, and perhaps also upon the erythrocytes, demands caution in its employment.—Ed.)

The course of the leukæmias is essentially chronic. In recent years, however, acute cases have been described which lead to exitus within a period of weeks, or even days.

The acute leukæmias are truly remarkable conditions characterized by a pronounced hemorrhagic diathesis and by an extremely rapid course. As fever is generally present, there may be a great resemblance to an acute infection. The leukæmic nature of the process consists in an increase in the white blood-cells and in an alteration in the types present. The number of leucocytes is highly variable and the increase is often insignificant. As a rule the predominating—sometimes practically the only—cell present

is a large mononuclear type[83] with an undifferentiated protoplasm, resembling the lymphoid mother-cell. In other cases, however, somewhat similar mononuclear cells suggest rather a myeloid origin. (These two cells are the lymphoblast and myeloblast, respectively, and the leukæmias themselves are known as acute lymphatic (lymphoid) and acute myeloid (myeloblastic).—Ed.) A classification of these acute conditions is, for the present, best not attempted, first because of the difficulty of distinguishing between these two types of large mononuclear cells; further, because in certain cases in which the cells in the blood were apparently lymphoid, no hyperplasia of the corresponding tissue was found; and finally because "mixed-cell" leukæmias occur, or one type may apparently go over into the other. The general tendency to-day is to catalogue the major part of these acute leukæmias as myeloid; for though the large cells of the latter are very similar to cells of lymphoid origin, yet the staining properties of the protoplasm are more suggestive of the forerunners of the myelocytes.

Two manifestations of leukæmia—the fever and the hemorrhages—are of particular interest. The temperature, which is often of a hectic type, cannot be explained on the basis of a complication. A tendency to hemorrhage into the skin, the choroid and the organs generally is particularly common in the acute leukæmias.

Both of these manifestations are important because of the possible relation they bear to the destruction of the blood-corpuscles. Hemorrhages and fever may also occur in pseudoleukæmia, the temperature at times assuming a characteristic relapsing character with periods of apyrexia (Ebstein).[84] (This type of fever is not present in aleukæmic leukæmias, but rather in those pseudoleukæmic types of a granulomatous nature, which will be discussed below.—Ed.) Pseudoleukæmia may also run a rapidly fatal course.

The chief feature, therefore, differentiating pseudoleukæmia from the ordinary types of leukæmia is the number of leucocytes in the unit-volume of blood. A conversion of a pseudoleukæmia into a true lymphatic leukæmia is very rare, although a few such cases have been reported. In one of these, a rupture of the hyperplastic tissue of a pseudoleukæmic gland into a vein could be

directly demonstrated, and coincidently a lymphatic leukæmia developed.[85] Nevertheless, border-line types of both leukæmia and pseudoleukæmia, as well as transitional forms, are surely very infrequent. Much more commonly, each disease runs a typical clinical course from beginning to end. Yet the two are doubtlessly closely related, being perhaps different forms of the same morbid process.

Of prime importance is the question of the relation which the changes in the spleen, the lymphatic apparatus and the bone-marrow bear to each other—and of the relation which these changes bear to the causation of the diseases under consideration. As a rule, all three of these organs are involved, usually in such a manner that the changes in two predominate. A normal bone-marrow is never present, though specific alterations may be absent. In some cases, the marrow changes can be recognized only with the microscope;[86] and not infrequently the bone-marrow is the only tissue involved.

Also of great importance is the question whether the anatomical changes in these organs are primary or secondary. This much is certain, that in lymphatic leukæmia and lymphatic pseudoleukæmia, the lymphadenoid tissue is hyperplastic, while in the myeloid forms, the bone-marrow elements are in a state of growth. If one regards these processes as affections of the myeloid and lymphoid systems respectively, the question as to the primary focus, from the general pathological point of view, is of no great moment,[87] for the disease may originate wherever there is lymphoid or myeloid tissue. In myeloid leukæmia, nevertheless, the tendency is to emphasize the crucial importance of the bone-marrow, because in adults this is the principal myeloid organ.

The conditions still grouped under the common caption **pseudoleukæmia** undoubtedly differ clinically in many particulars. The recent tendency[88] is to separate those on an infectious (granulomatous) basis from others hyperplastic in character. The last only are leukæmic in nature, differing from the usual leukæmias, as has already been stated, merely in the absence of leukæmic elements in the circulating blood.

(A great deal of attention has been devoted in recent years to that type of pseudoleukæmia belonging properly, it would seem, to the granulomas, and known otherwise as **Hodgkin's disease** or **malignant granuloma.**[89] This does not include the varieties due

to syphilis or to tuberculosis in its usual form. Clinically, it may be indistinguishable from the true pseudoleukæmias (aleukæmic leukæmias) on the one hand, and from neoplastic growths on the other. The microscopic examination, however, usually makes a diagnosis possible, revealing changes more or less constantly observed, but variously interpreted. Sternberg regards the condition as **a peculiar form of tuberculosis** and finds an unusual type of giant-cell, to which Reed[90] has also called attention. Frænkel and Much[91] consider the disease to be due to a granular form of the tubercle bacillus which appears only with a special staining technic. More recently, Bunting and Yates and others[92] have isolated a pleomorphic diphtheroid bacillus from the affected lymph-nodes, by means of which they state that they have transferred the disease to rhesus monkeys. The former also describes a characteristic blood-picture for the disease.[93] The monograph of Kurt Ziegler will give the reader a comprehensive insight into the present conceptions of the condition.—Ed.)

Kundrat's lymphosarcoma occupies a peculiar position among the pseudoleukæmias. The localized swellings of the lymph-nodes which characterize it are genuine neoplasms. This condition, therefore, both etiologically and pathologically, is an entity, and a third type of pseudoleukæmia. The microscopic examination of a specimen of excised node may be essential to distinguish this from the other two forms of pseudoleukæmia.

In lymphoid leukæmia, the lymphatic tissues of the lymph-glands, the spleen, the intestines or of the bone-marrow, are increased. Whether the lymphocytes present in the blood originate solely from the bone-marrow, or from the various collections of lymphoid cells throughout the body, is not yet definitely known. It is of considerable interest, however, that instances of lymphatic leukæmia without enlargement of the lymph-glands have been reported. Such cases demonstrate how careful we must be not to assume that lymphatic leukæmia is essentially a disease of the lymphatic glands. It seems more probable, indeed, that it is primarily a disease of the lymphoid tissue of the bone-marrow, though recent work has shown that numerous mitoses may be present in other organs; and it is quite possible that white corpuscles may arise in tissues which normally produced these cells only during embryonic life, as, for example, the liver.

In regard to the nature of the pathological process in leukæmia, we wish again to recall the observation from Marchand's laboratory on a case of lymphatic leukæmia which apparently originated from the rupture of a hyperplastic lymphatic gland into a vein. Many facts favor the view that a growth of cells into the blood-stream is the cause of the blood-changes in leukæmia. Thus, as illustrated, pseudoleukæmia may change into a true leukæmia by the rupture of a hyperplastic gland into the circulation.

This is readily understood because hyperplasias of myeloid and lymphoid tissues give rise to tumor-like growths (possibly of infectious origin).[94] In the present opinion of most observers, however, the leukæmias are to be separated from the genuine tumors.[95] Since the conditions in the bone-marrow especially favor such a rupture into the blood-stream, pathological changes in this tissue are most apt to give rise to leukæmia.

The theory that leukæmia is due, not to an excessive production, but to a diminished destruction of the leucocytes, deserves to be considered merely to be condemned, for it has been proved that the destruction of these cells, far from being decreased, is actually increased. Many leucocytes may be seen in blood-preparations in various stages of degeneration, and the increased elimination of uric acid and of the xanthin bases in the urine indicates an increased destruction of the nucleoproteids of the body, which are derived, in all probability, from the nuclei of the leucocytes (see p. 365).

Toxic influences also play an undoubted part in the pathology of leukæmia. Speaking for this are the peculiar forms of retinitis occasionally seen; further, a characteristic nephritis; and also degenerative changes in the central nervous system.

The ultimate cause of leukæmia and pseudoleukæmia is still unknown. It is possible that the recent experimental production of the disease in birds by the injection of leukæmic blood[96] may pave the way for a fuller understanding of the conditions.

Plasma and Serum. The Total Quantity of Blood

Little is known about pure plasma, principally because it is so difficult to preserve it without coagulation. The serum resulting from coagulation differs from the plasma within the blood-vessels in that it contains no fibrinogen, but does contain fibringlobulin

and the fibrin ferment. Probably other changes, at present but little understood, also take place in the proteids of the blood during coagulation.

Coagulation.—When normal blood coagulates, about 0.1 to 0.4 per cent. of its weight separates as fibrin. This may be pathologically increased up to 1.0 or 1.3 per cent., an increase which is seen especially in diseases accompanied by inflammatory exudations, such as pneumonia, pleurisy and acute articular rheumatism. In other infections, notably in typhoid fever, this increase of fibrin is not found. There exists a certain parallelism between the number of leucocytes and the amount of fibrin in the blood, but the parallelism is by no means a strict one,[97] and in leukæmia the fibrin may not be increased at all.[98]

In other diseases the quantity of fibrin in the blood is diminished; and in a case of hemorrhagic smallpox, for example, no fibrin could be obtained. The same has been noted in phosphorus poisoning. Diminution of fibrin is usually found in severe infections and in severe injuries to the general nutrition, as in septicæmias, long-continued suppurations, anæmias, etc.

Our knowledge[99] of the physiology of **blood-coagulation** is still so limited that it would be hazardous to speculate on the significance of pathological variations in the amount of fibrin in the blood and the effect that these variations have upon coagulation. It has been assumed that if the amount of fibrin be diminished, the blood will coagulate slowly and there will be a tendency to hemorrhages; whereas, if the amount be increased, coagulation will be rapid and there will be a tendency to thrombosis. These assumptions, however, are not sufficiently supported by facts.

Disturbances of coagulability[100] have been generally assumed to explain the family disease of hæmophilia. As a matter of fact, Sahli[101] was able to demonstrate that the coagulation time between the periods of hemorrhage was slower in these patients than normal; but that during the hemorrhages it was not particularly slow. He is inclined to attribute the bleeding of hæmophilics to lesions of the vessel walls, which on the one hand tear with abnormal ease and on the other yield too little of a substance that is necessary for coagulation (thrombokinase).

The Blood-Serum.—All substances formed in the metabolic processes within the body and all food-stuffs introduced from without pass through the blood; they may, however, be present there

only in minute traces, because they are so quickly removed by the various organs. It would be impossible to discuss in this place all those conditions in which some constituent or other of the serum is changed, as happens, for example, in diabetes, and it seems better to reserve such a discussion for the chapters on metabolic disorders.

One substance, however, may be mentioned in this connection, *viz.*, fat. Fatty substances are constantly present in the blood,[102] the amount being increased during the digestion of meals containing much fat. Under pathological conditions, the quantity of fat in the blood may become so great—even up to 20 per cent.—that particles can be recognized microscopically between the red corpuscles, especially if they have been stained by osmic acid.[103] This condition, known as lipæmia, is relatively uncommon. It occurs in various pathological conditions, especially in diabetes, and is frequently merely transitory.

In discussing the chemistry of the blood-serum, we shall consider especially the proportions of proteids, salts and water. According to Hammarsten's analyses, 9.2 per cent. of the serum consists of solids, of which 7.6 per cent. are proteids. Since the proteids form the greater part of the solid material in the serum, they and the water ordinarily vary in inverse ratio to each other, a high percentage of proteids being accompanied by a relatively low percentage of water, and *vice versa*.

The proteids of the serum consist chemically of albumin and various forms of globulin. Recent biological work, however, has shown such a variety in the proteids of the blood that we can no longer regard the above simple chemical division as in any way a final one; and when we remember that in all probability each organ contributes its quota to the blood, it seems impossible that the division into the albumin and globulins could be any other than a mere classification of the proteids present under these group names. The serum of healthy men contains somewhat more albumin than globulin, the ratio being about 4.5 to 3.1. This ratio differs in different species of animals,[104] and varies in the same individual under different circumstances. During fasting, the globulins become relatively increased to a slight extent.

Our knowledge of the proteids of the blood has undergone a complete revolution within recent years.[105] The researches on

immunity have brought to light important functions of the blood which were hardly suspected previously. The substances which bring about these so-called biological reactions cannot be separated from the proteids by purely chemical means, though we have no direct proof that they are themselves of a proteid nature.

Among the substances under consideration are those which possess the property of accelerating the decomposition of other compounds, *i.e.*, they are of the nature of ferments. If we may assume that the decomposition of different compounds requires the action of different ferments, then the number of ferments present in the blood must be considerable. Some of these are proteolytic, some amylolytic, others oxydases and coagulating enzymes.[106]

Recent studies indicate the presence also of numerous antiferments. Whether these are actually antibodies, or merely the products of the action of colloids upon the ferments, is not definitely known. Antiferments occur normally in the blood of healthy individuals and may also be produced by the injection of ferments, in the nature of an immunization. Particular interest has lately been directed to the subject of antitrypsin, which is often abundantly present in the cachexias.[107]

Besides the proteids there are many other nitrogenous substances regularly present in small amounts in the serum, with many of which we are still unfamiliar. Taken together they are known as the residual or non-coagulable nitrogen.[108] This residue is comprised chiefly of the end-products of metabolism, substances which go over into urea, and are ordinarily removed by the urine. They are increased, therefore, when elimination is imperfect—for example, in nephritis, uræmia and in different febrile conditions. In great part such an increase is to be attributed to urea retention. (The importance of this in modern renal functional tests will be considered in Chapter XI.—Ed.) The entire fabric of proteid metabolism would reveal itself if the building-stones of the proteids—the amino-acids and similar bodies—could be isolated from the blood, and especially from the intestinal veins.

In processes such as phosphorus poisoning, accompanied by considerable tissue necrosis, amino-acids have been found in the blood, but here the proteid split-products have naturally no relation to digestive processes. Recently Bingel[109] has demonstrated

glycocoll in normal serum, a discovery possibly significant in view of what has been said.

(Considerable progress, indeed, has been made along these very lines. Abderhalden,[110] using enormous amounts of blood at a time, has succeeded in demonstrating the presence of amino-acids in the serum by the direct isolation and identification of a number of these proteid split-products. As the blood contains these acids even in starvation, Abderhalden conceives of the possibility of a fixed amino-acid content, comparable in a way to the constant sugar concentration.

More recently Abel, Rowntree and Turner[111] have isolated from the blood, by a process of dialysis, two amino-acid derivatives of proteid—alanin and valin—in crystalline form. By the same method they have identified histidin and creatinin and lactic and beta-oxybutyric acids.—ED.)

The Salts of the Serum.—The salts of the serum are for the most part made up of sodium chlorid, sodium carbonate and the phosphates of the alkalies. Other salts are present only in minimal quantities, and some, such as calcium phosphate, are present in the plasma, but are removed from the serum by the fibrin during coagulation. The variations of the salts of the blood in health and in disease have never been satisfactorily worked out.[112] This is unfortunate, for, without doubt, they exercise an important influence upon the blood-corpuscles and upon the proteids of the plasma. The maintenance of the molecular concentration of the serum at a constant level, as determined by cryoscopy, is extremely important.[113]

The Percentage of Water in the Blood. Hydræmia.—The relative amounts of proteids and water in the serum vary even in health, although the limits of these variations are not accurately known. The variations in disease have been only incompletely studied;[114] but we know that they frequently remain within the normal limits, even in the severest diseases. The most evident thickening of the blood, *i.e.*, the greatest relative increase in the proteids, is seen in Asiatic cholera, and depends upon the loss of fluids from the body.

When the unit of blood is deficient in proteid material, we speak of an hydræmia, or a watering of the plasma.[115] This condition frequently develops as a result of emaciating diseases. If the heart and kidneys are in order, the hydræmia

is probably due to a primary diminution in the proteids of the blood, although we must remember that a destruction of the proteids of the body does not necessarily produce a watery condition of the plasma. Among the emaciating diseases which may cause an hydræmia of this character are inanition, repeated hemorrhages, anæmias, malignant tumors and severe chronic infections. Although an hydræmia frequently develops in the above conditions, it does not necessarily do so. We are not justified, therefore, in concluding that a rapid consumption or a diminished supply of proteid material is alone responsible for the hydræmias of this class. Other factors, at present little understood, undoubtedly play a part. Until we know more of the functions and source of the proteids of the plasma, it will be impossible to harmonize the many contradictory facts relating to this class of hydræmias.

It is possible that an hydræmia may be caused not only by a primary reduction of the proteid constituents of the blood, but also by a primary increase in the amount of water. The hydræmias associated with the diseases of the kidneys and with cardiac insufficiencies are probably in part of this nature. According to Hammerschlag, chronic interstitial nephritis rarely causes a watery condition of the blood, and chronic parenchymatous nephritis sometimes fails to do so. Hydræmia is frequently present in the latter, however, and it is most marked when there is polyuria. Under such circumstances, the specific gravity of the blood may fall from the normal of 1.030 to 1.020. Other observers have obtained results which differ somewhat from those of Hammerschlag; yet some of these, based upon total nitrogen determinations, must be rejected as inaccurate on account of the frequent retention in nephritic blood of other nitrogenous bodies than proteids.

The hydræmia which is undoubtedly present in many cases of nephritis can be caused only in part by the loss of albumin, for the hydræmia and the amount of albumin in the urine bear no definite relation to each other. In many cases of nephritis, water is retained in the body, for less is excreted through the kidneys, and often less also through the skin. These two factors —the loss of albumin in the urine and the retention of water in the body—are sufficient to explain the hydræmia present in many cases of nephritis, though hardly in all, for some patients with

hydræmia are excreting large amounts of urine. Recent studies[116] attribute the retention of water to a deficient sodium chlorid elimination, the retained water serving merely to restore the balance of osmotic tension. To what extent variations in the colloids—in this case the proteids of the serum—are influential in water retention, is a question that, for the present, cannot be answered. (See p. 93 in chapter on œdema.)

Certain patients, suffering from heart disease in the stage of broken compensation, show a watery condition of the blood—both the specific gravity and the proportion of proteids in the blood being diminished. A weakness of the right ventricle is apparently the prime factor in the production of such an hydræmia.[117] When the circulation improves and the venous pressure falls, the blood tends to return to its normal composition. This hydræmia occurs in a comparatively small proportion of all cases of broken compensation; but, where it does occur, it usually disappears with an improvement in the circulation. In these cases, the loss of proteids from the blood is ordinarily not very great, but there is frequently a retention of water which would tend to dilute the blood.

It seems very probable to us that the hydræmias which accompany cardiac and renal diseases are for the most part caused by such a retention of water in the body; that there is, in fact, an increased quantity of watery blood in the body, a so-called hydræmic plethora. Such an hypothesis would well explain the fact that with the development of cardiac insufficiency not only the proteids, but the number of corpuscles to the unit-volume of blood, are diminished, and that, with an improvement in the circulation, the blood again becomes normal. There is no reason why the blood should not become œdematous just as do the tissues. Possibly the water is held back in the body by substances which attract it (see above). Grawitz believes that the increased amount of water in the blood is derived from the lymph which diffuses into the capillaries, owing to the low pressure existing there. Yet we know that in the conditions under consideration, fluids pass from the capillaries into the lymph-spaces, so that these become distended. The relations must, therefore, be quite complicated, and the final results are dependent upon which process takes place the more rapidly.

Polycythæmia.—In not a few cases of chronic stasis, the capillary blood is more concentrated than normal. At least it contains many more red blood-corpuscles and correspondingly more hæmoglobin to the unit-volume. The composition of the serum in these cases has not yet been finally settled, but good observers[118] have found it to be diluted. This increase in the number of the erythrocytes is found especially in cases of long-continued venous stasis, such as occurs in congenital heart lesions, in chronic pulmonary disease and in insufficiency of the right ventricle. Investigations thus far have all been made upon the blood of the cutaneous capillaries or veins, so that we are unable to discuss the relative concentration of the blood in the different vessels of the body. The observations of Askanazy, however, would indicate that conditions are the same in the visceral as in the peripheral vessels—that is, that the polycythæmia is general.

The number of erythrocytes in these cases is often very great—from six to even twelve million per cubic millimetre; and at the same time the serum is usually more dilute than normal. This latter fact would seem to indicate that the increased number of corpuscles is not due to a loss of water from the blood. Marie and Hayem explain the increase in the number of red blood-corpuscles as a compensatory process which tends to neutralize the insufficient oxidation of the blood caused by the stasis.[119]

There is another form[120] of polycythæmia, apparently primary in nature, in which the corpuscular increase is persistent. This type (polycythæmia rubra vera), first described by Vaquez, regularly shows an increase in the red corpuscles, as high often as ten million per cubic millimetre. This condition is due, in all probability, to an increased formation of red cells, rather than to a retarded degeneration, in view of the presence of nucleated erythrocytes and of myelocytes in the blood (Türk), and because of the finding of a hyperplastic red bone-marrow. In many cases, in addition to the polycythæmia, there is present also an enlargement of the spleen and liver and an increased arterial tension (Geisböck). It is possible that nephritis and arteriosclerosis play a part in the hypertension cases. The causes of this primary polycythæmia are unknown. The theory that the hæmoglobin is primarily at fault and that its lessened oxygen-carrying power necessitates a compensatory increase in the red cells is hardly

tenable. In the author's case, indeed, there was an *increased* gaseous interchange in the tissues. A more probable explanation is that the condition depends upon a hyperplasia of the red marrow, of unknown origin.

Extremely interesting are the changes which take place in the blood when an animal passes from a region of high to one of low atmospheric pressure.[121] Within a short period of time, the number of red corpuscles to the cubic millimetre of blood is increased, and the hæmoglobin likewise, but more slowly. These changes affect the blood in all parts of the circulatory apparatus, though they are less marked, possibly, in the arteries than in the veins and capillaries of the skin. The higher the elevation, the greater is the number of red corpuscles. The highest figures which have been reported are from the Cordilleras, at an elevation of over twelve thousand feet. All the animals at these heights have an extraordinary number of red corpuscles—the llama, for example, having sixteen million to the cubic millimetre. The amount of oxygen in the blood, however, is about the same as in that of animals at lower levels. When a man or animal descends from these heights to the sea level, the number of red cells diminishes correspondingly. There is almost universal agreement among authors in regard to the increase in the number of erythrocytes per unit-volume at high elevations, and the few negative observations are due probably to too short a stay at the high altitude, or to complicating conditions, such as mountain sickness.

This increase is unquestionably caused by the low atmospheric pressure, for it can be produced experimentally by subjecting animals to low pressures under the air-pump. Some consider that the total number of red cells in the body is actually increased in such cases, and that this serves to compensate for the lessened pressure of the oxygen in the lungs. If, indeed, new cells are formed, we have little microscopical evidence of it, for nucleated red corpuscles have been seen by very few, and most authors expressly state that they were absent. Furthermore, it is difficult on such an hypothesis to account for the rapid disappearance of red cells when the animal returns to a lower altitude, for positive signs of a destruction of red corpuscles, such as jaundice and a deposition of iron in the liver, have not been observed under these conditions.

Yet we know that the absence of these signs is by no means absolute proof that no destruction of the red cells has taken place, for they have been missed in cases in which an extensive destruction certainly had occurred.

Another explanation that has been offered for the increase in the number of the erythrocytes at high altitudes is that it is due to a loss of water from the blood; yet this meets with almost equal difficulties. Beyond question, the dryness of the air, the exposure to the sun's rays, and the deeper respirations increase the loss of water from the body, yet a healthy man would ordinarily replace this water by taking more fluids by the mouth. The supposed loss of water should also lead to a more concentrated serum, as well as to an increased number of red blood-corpuscles; but it is very doubtful if this concentration of the serum actually occurs. The sera of two rabbits in Basel contained 7.62 and 7.96 per cent. of solids respectively, whereas in Arosa, at a high elevation, the percentages were 7.79 and 8.02, an inconsiderable change compared with the changes in the erythrocytes. Grawitz found some increased concentration in the sera of animals which had been kept under low pressures in Berlin, but here again the increased concentration was in no way proportional to the increase in the number of the red blood-corpuscles. Furthermore, a concentration of the blood by evaporation is only possible when the tissues likewise lose large quantities of water, and such a loss of weight certainly does not occur either in men or in animals subjected to low atmospheric pressures. Finally, an increase in the number of erythrocytes also takes place when the animals are prevented from losing excessive amounts of water by being kept in rarefied air saturated with water vapor.

According to a third theory, the increase in the number of red blood-corpuscles at high elevations is due to the passage of plasma out of the blood-vessels into the lymphatic system. At present, this seems to be the most plausible explanation for the known facts; yet it is also open to objections, especially in view of the fact that the red blood-corpuscles and the hæmoglobin do not increase at precisely the same rate.

The crucial test for deciding whether or not the hæmoglobin actually increases at high altitudes would be the determination of the total quantity of hæmoglobin in the body. If this be increased in animals exposed to low atmospheric pressures, we may

then assume that there is indeed a total increase in the red blood-cells and in their pigment under these influences. Unfortunately, the experiments which have been undertaken to decide this point have given contradictory results. Some observers found no increase in the total amount of hæmoglobin in the body, others have found a slight increase, while still others have found a marked increase. The inaccuracies in the methods for determining the total hæmoglobin in the body probably account for these discrepancies in results.

An increase in the number of the red blood-corpuscles to the unit-volume is also seen in phosphorous and carbon monoxide poisoning, but we are ignorant as to its exact cause.

Plethora.—There is no reason *a priori* why an increase in the total quantity of blood in the body should not take place,[122] for it is known that the parenchyma of other organs may increase in bulk. It is impossible, however, to obtain direct proof of such an increase so far as human blood is concerned, for as yet we have no accurate method of determining the total quantity of the blood in man.

The doctrine of an increased quantity of blood—a true plethora—played a great rôle in the older hæmatology, and various symptoms were believed to be caused by the "full-blooded" condition of the patient. While we must acknowledge that many of these cases will not stand the rigid criticism of modern times, and that the anæmia of many of these individuals was the probable cause of their symptoms, yet there are certain facts which favor a belief in the occurrence of a true plethora. Thus, many patients feel better after having been bled, and although this fact is in no sense a proof that a condition of plethora existed previous to the bleeding, nevertheless it cannot be entirely disregarded. More important is the testimony of such pathologists as v. Recklinghausen and Bollinger, who give it as their impression that at autopsy many bodies seem abnormally rich in blood. That the amount of blood in animals may vary greatly not only in different species, but in different individuals of the same species, has been definitely proved by the work of Bergmann and Bollinger. They have demonstrated that the character of the food may exert a marked influence upon the total quantity of blood in the bodies of animals.

We are justified in suspecting a condition of plethora whenever

an individual who habitually consumes excessive amounts of food and drink, and who has large muscles and much fat, shows a continued hyperæmia of the surface of his body, and has an enlarged heart, a full pulse and wide arteries. Although we may be unable to prove that a plethora exists in such individuals, nevertheless the experience of pathologists, and the experimental evidence above referred to, both justify such a probable diagnosis. The interesting observations of Geisböck[123] would indicate that a plethora of this kind may accompany a condition of hyperglobulism and increased blood-pressure (polycythæmia hypertonica).

Certain observations seem opposed to the doctrine of plethora, more especially the fact that if animals are infused with sera or salt solution, the excess of fluid is rapidly removed from the circulation, and no increase in the total quantity of blood is produced. Yet the conditions of such an experiment are quite different from the chronic changes which are believed to lead to plethora in man; and, furthermore, it is quite possible that under pathological conditions the ability thus to remove large quantities of fluid from the circulation may be lost.

We hold, therefore, that although the doctrine of a true plethora has not been absolutely proved, its existence is very probable. The long-continued ingestion of excessive amounts of food seems to be the most potent causative factor. Yet it is apparently only one factor, and others of which we are now ignorant may play a part in its causation.

Until recently, the doctrine of a diminution in the total quantity of blood was as little capable of direct proof as was the doctrine of plethora. The improvements in the methods[124] for the determination of the total blood mass have brought with them a greater accuracy in this respect, with the result that clinicians, as well as pathologists, have been strengthened in their belief that a plethora does exist. Especially interesting is the plethora of chlorosis, nephritis and of polycythæmia. In severe anæmias, on the contrary, there would appear to be a diminution not only in the number of cells to the unit of volume, but in the quantity of blood as a whole.

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CHAPTER III

INFECTION AND IMMUNITY

(With the Collaboration of Dr. E. Levy, Strassburg)

In this chapter we purpose considering the various means by which the animal body resists the invasion of pathogenic micro-organisms.[1]

The Portals of Entry.—How bacteria, under ordinary conditions, gain entrance to the body is still not definitely known. The body-surfaces are constantly beset by innumerable micro-organisms, among them the ordinary agents of inflammation and suppuration: they are present on the skin, in the nose and mouth, in the trachea and gastro-intestinal tract, and in the vagina and urethra. Despite their intimate relation to the major part of those surfaces which lie between the organs and the outer world, they seldom gain access to the former; at least, according to our present conception, morbid processes are initiated with relative infrequency by bacteria which are normally present on these surfaces.

It is evident, therefore, that some protective mechanism holds the organisms in check—this protective function, without doubt, residing in the cells which constitute these surfaces (see below); for the normal epithelium of the skin and of the respiratory and digestive tracts is able, as a rule, to prevent the invasion of micro-organisms.

Solid particles other than bacteria encounter an equal difficulty. In the case of mercurial ointment, which seems to be an exception to this rule, soluble fatty-acid salts[2] are no doubt formed on the skin in a manner analogous to the emulsification of fat before its absorption by the intestines. In view of the fact that leucocytes can pass between the epithelial cells, it is possible that they may carry back with them bacteria which they have taken up on the body-surfaces. Were this true, it would indeed be a marvellous process, for the body would thereby infect itself. The ingested bacteria would, undoubtedly, be destroyed in many instances by the white cells; yet this would not be the case in aerogenic tuberculosis of the bronchial lymph-nodes. Here the

survival of the bacteria, *per se,* might be regarded as evidence of the disease and indeed its very incipiency. And in the present status of our knowledge this would actually seem to be true.

This migration of the leucocytes might have a double purpose: first, to carry to the organs the solid portions of the food, and secondly, to take up the bacteria similarly as solid particles, relying upon their ability to destroy them. Such a mechanism would be advantageous to the body, in that, without danger, it could protect itself against certain micro-organisms.

The acute infections due to the entrance of bacteria through the skin presuppose an injury to the epithelium, which may, however, be insignificant.[3] Thus Garré was able to produce a genuine furuncle on his left arm by rubbing staphylococcus pyogenes into the skin; and guinea-pigs may be infected with plague by rubbing the cultures into the freshly-shaved skin. The minimal injury to the epithelium in both of these examples enabled the micro-organisms to enter.

Our knowledge of the method by which infections enter through the mucous membranes is very limited. Tonsillar diseases appear to play an important rôle in predisposing to infections with the pyogenic cocci. The wandering of the leucocytes through the epithelium of the tonsils, and the frequent local lesions, render them especially permeable to bacteria, and in turn to a general bacteræmia.

The nose, with the accessory sinuses and the nasopharynx, catches and holds in its numerous corners and folds the micro-organisms that enter. Its lymphatic tissues, and especially the nasal tonsil, are exposed to the same dangers as are the faucial tonsils. The secretions of the nose are bactericidal; but in the rat, at least, this does not afford efficient protection against plague bacilli, for the introduction of a few of the latter into the nose of this animal will lead to a fatal infection.

(The importance of so-called **focal infections** [4] has only recently, it would seem, received the emphasis it deserves. That a systemic or localized disease may arise on the basis of a pre-existing sluggish, or even latent, infectious focus, has long been known. It is to clinical and experimental observations of the last few years, however, that we owe a better understanding of the part these infections play in pathological processes.

The focus is most commonly located in the head, the ton-

sils and the lymphatic tissues of the nasopharynx being the favorite sites. An infected tonsillar crypt, often in a deeply buried organ, which may have caused few if any symptoms, is a frequent finding. Chronic alveolar abscess, infections of the nasal sinuses, of the middle ear and mastoid, and less often of the gall-bladder, appendix or prostate, may be foci in other cases.

The morbid processes induced by bacteria, or bacterial toxins, emanating from these sources are manifold; and they may be acute or chronic in nature. To the former belong rheumatic fever, endocarditis, both ulcerative and benign, and the different bacteræmias; to the latter, chronic arthritis (often the so-called arthritis deformans), myocarditis, nephritis and degenerative changes in the vessel-walls.

The brilliant results in many cases following the surgical removal of the offending focus speak forcefully for the correctness of this conception of the significance of focal infections.

It was in connection with his studies on focal infections that Rosenow[5] elaborated his view of mutation in the streptococcus-pneumococcus group. This would say, in brief, that the streptococcus, the organism most frequently concerned in these infections, may undergo changes in pathogenicity and in cultural characteristics by a variation in the conditions of growth and by animal passage. Thus in one phase of mutation the streptococcus may cause an arthritis, in another an endocarditis, and in still another a pneumonia. The production of acute gastric ulcer,[6] as a mutation phase, will be discussed in another place.—Ed.)

The air-passages of healthy individuals, below the upper part of the trachea, are generally considered sterile; only on forced inspiration may bacteria penetrate to the finer bronchi. Should the bacteria penetrate to the alveoli themselves, the delicate epithelium of the air-cells would hardly prevent them from passing through, for we know that solid particles, if inhaled in great numbers, such as occurs in the dust-diseases, are often deposited in the pulmonary tissues. Many observers believe that bacteria may similarly enter the lungs if they are sufficiently numerous in the inspired air. Such invaders may cause diseases of the lungs themselves, or they may be carried to the neighboring lymph-nodes, there to multiply, or to be destroyed or to remain latent. The lungs seem to be well equipped to destroy bacteria that may

reach them, and even though they become inflamed, this inflammation may protect the rest of the body from a general invasion. Indeed, it seems to be rare for a general infection to gain admittance to the body via the lungs, without causing a primary disease of these organs or of their lymphatic apparatus.

The factors which favor an infection of the air-passages have been accurately determined in animals,[7] much more so, indeed, than in man. A large number of micro-organisms in the inspired air undoubtedly favors infection, especially if the individual breathes deeply. These bacteria may be present not only in dry dust, but may be carried by minute moist droplets which have been thrown out into the air by other persons in coughing, sneezing or talking.[8] Infection of the lungs may also be induced by the aspiration of substances, such as food and water, carrying bacteria in with them.

The virulence of the bacteria inhaled is also of importance, as is likewise an inflammation of the upper air-passages, which favors the migration of micro-organisms into the lungs. Exposure to cold and to dampness is generally believed to predispose to the development of infectious processes in the bronchi and lungs, possibly by lowering the resistance of the epithelial linings. If the inspired air is not filtered by passage through the winding upper respiratory tract, infection of the lungs is directly favored; for this reason a tracheal cannula is always a menace. Animals with weak respiratory muscles are practically certain to die if they breathe through such a cannula; and, for the same reason, inflammations of the air-passages are relatively frequent in mouth-breathers.

The gastro-intestinal tract is continually receiving micro-organisms which have been swallowed in the food and saliva. Some of these are quickly destroyed by the action of the hydrochloric acid; yet since the stomach begins to empty itself shortly after the food enters, and since the acid first secreted is bound by the proteids of the food, and since, finally, the gastric juice does not penetrate the interior of many large food particles, the possibility always exists that virulent organisms will pass through the stomach into the intestines.

As to the bowel itself, it may be said, in general, that solid particles, without amœboid movements, are unable to penetrate the intact mucous membrane, even fat first requiring emulsifi-

cation. Though phagocytic white cells are able to pass between the epithelial cells, it is still undetermined whether they can carry back with them solid substances. It is possible that micro-organisms penetrate the bowel wall in some way peculiar to themselves. That penetration does occur is illustrated in the case of cholera, of tuberculosis and of trypanosomiasis. The crucial question is whether the organisms can pass through an intact epithelium or must first injure the latter in such a way as to facilitate their entrance. Ficker[9] found in rabbits, dogs and cats of the suckling age that the normal epithelium was no barrier to the passage of bacteria, while in adults of the same species, a certain period of fasting was necessary to render the epithelium permeable. Hard work, thirst, and inflammatory changes in the intestinal lining are all factors favoring the penetration not only of micro-organisms, but also of proteid substances, ferments and toxins, according to Holle.[10]

Baumgarten[11] has shown experimentally that tubercle bacilli rapidly disappear from the intestinal contents, and that a few may afterwards be found in the lymphatic follicles and nodes of the intestines, having been carried in, in all likelihood, during the absorption of fluid. As the tubercle bacilli are not motile, and as there is no evidence that the leucocytes have carried the bacilli through the mucosa, the conception of a transportation by the fluids absorbed seems not unlikely, particularly in view of the very low specific gravity of the Koch bacillus.

It is not impossible that the mode of penetration is peculiar to the organism. Thus the typhoid bacillus and the cholera vibrio multiply prodigiously in the lumen before invading the mucosa, thereby possibly producing toxins which first injure the epithelium and pave the way. In dogs, for example, the congestion caused by podophyllin renders the intestinal lining permeable to bacteria.[12] And, finally, the possibility of organisms entering the blood during digestion has never been disproved.

Granting that bacteria can penetrate the intact intestinal wall, they certainly cannot do this easily, and many circumstances influence the process. In the first place, the *number of bacteria present* is of great importance. Then, too, a *rapid transit through the intestines* may serve as a protection against invasion. Possibly this is the reason that many diseases of the intestines, such as typhoid fever, affect principally

the ileum, where peristalsis is slower than in the jejunum, and where the organisms have a better chance to cling to the walls and multiply. Furthermore, as is well known, the normal flora of the intestines may cause strange bacteria to disappear by outgrowing them; and thus many pathogenic micro-organisms, if introduced into the intestines, rapidly disappear without producing symptoms. Finally, the normal mucous membrane seems to have the property of exerting a destructive influence upon the micro-organisms in the intestinal canal.[13] Toxins, excepting that of botulism, are not absorbed by the normal mucosa of the bowel; they are either destroyed or rendered non-toxic by the digestive ferments.

Conditions in the vagina are somewhat similar to those in the bowel. There, also, we have a normal flora, which may injure strange invaders; while the acid reaction of the secretions of the vagina is unfavorable to the development of most pathogenic bacteria.

It is evident from all that has been said, that numerous defenses against the invasion of micro-organisms are present on the surfaces of the body. The difficulty of passing the intact epithelium, the acidity and bactericidal properties of many of the secretions, the conflict with the normal flora—all of these serve to protect the body against bacterial invasion. The very efficacy of these barriers resides, it would seem, in their complexity. v. Behring[14] has called attention to the fact that an animal may be highly susceptible to inoculation with a micro-organism and yet be quite insusceptible to the corresponding natural disease, apparently because it is able to prevent the entrance of the organism into its body (mouse anthrax, guinea-pig tuberculosis). Infection under natural conditions is, therefore, a complicated process and points to the breaking down of the defensive forces at the body surfaces.

The Factors Determining the Character of an Infection.—The manifestations of infection vary considerably, depending upon the virulence of the invading organisms, the number of the latter, their toxicity, the portal of entry and the resistance of the individual.

Upon what factors the virulence of micro-organisms depends

is only partly understood. With a few exceptions, such as anthrax and plague, the virulence varies considerably from time to time, and even during the course of a single infection. As a rule, it increases up to the height of a disease and diminishes with convalescence. Organisms possessing capsules are in general less readily destroyed than those without. Bail and his co-workers [15] believe that the virulence of bacteria depends upon substances they secrete, called by them aggressins, which keep the phagocytes at a distance. This conception, however, is by no means generally held. Though the contagiousness of a disease ordinarily runs hand in hand with the virulence of the causative organism, this need not be true, as is proved by an epidemic of typhoid fever which we observed. The mode of transmission was by direct contact, and in the seventy cases there were no deaths, despite the fact that the majority were in children and many in enfeebled individuals.

The number of micro-organisms introduced into the body is also of great importance. A certain number of even highly virulent bacteria is necessary in order to cause a fatal infection. This minimum lethal dose varies indirectly as the resistance of the animal and directly with the virulence of the bacteria. Only a very few of the most virulent may be necessary to infect highly susceptible animals. If more are introduced, the period of incubation becomes shorter and death follows more quickly.

The portal of entry of infecting organisms influences both the character and the course of the infection. If bacteria are introduced directly into the blood-stream, as happens in general infections with the pus cocci, or with the bacilli of anthrax or tuberculosis, the resulting disease runs a stormy course. Furthermore, the same staphylococci which will cause a pyæmia if introduced into a vein, usually produce only a local lesion if injected subcutaneously. There are indeed exceptions to this general rule. Cattle, for example, are readily infected with rauschbrand subcutaneously, but withstand intravenous injections of the same material; and man is most susceptible to the cholera vibrio when the latter is in the gastro-intestinal tract.

The virulence of infecting micro-organisms, and their tendency to cause a general intoxication, depend to a great extent upon the **toxins** they produce. In the case of the diphtheria and tetanus bacilli these toxins pass into solution; and filtered cultures containing these soluble poisons give rise to the same symptoms as

do the bacilli themselves. The bacterial toxins resemble ferments in many ways, for example, in their susceptibility to moist heat, to light, to oxygen, etc. Their extreme potency, exceeding that of any other known substance, also suggests a relationship to the enzymes.

The method of dissemination of tetanus toxin is quite unlike that of any known alkaloidal poison, such as strychnin, for example. The latter is carried to the susceptible cells by the blood-current, whereas tetanus toxin travels through the nerves from the point of infection to the central ganglion cells, upon which it exerts its poisonous action.[16] These ganglion cells cannot be reached directly by way of the blood or lymph, though they are affected by injections of the toxins directly into the nerves or into the spinal cord. It is this mode of diffusion of the tetanus toxin that renders so unsatisfactory the specific therapy of the disease. (Recent clinical and experimental studies[17] point the way to a more rational and successful treatment of tetanus. The use of antitoxin as early as possible, and the employment of a sufficiently large dosage—injected at the outset intravenously and intraspinously, and later subcutaneously, in order to maintain the antitoxin content of the blood at an efficient level—have materially lowered the mortality statistics of those who have employed this method.—Ed.)

When the injections of tetanus toxin are made into the cord, the incubation period intervening before the development of symptoms, which is otherwise so prolonged in tetanus, is much shortened or entirely absent. The incubation period for tetanus, therefore, appears to be the time consumed by the toxin in travelling from the point at which it enters the body to the cells upon which it exerts its poisonous action. This mode of dissemination explains the fact that in experimental tetanus the spasm first develops in the extremity infected; for the toxin travelling up the nerve, first acts upon the corresponding part of the cord. In man, however, the muscles of the jaw are usually first affected. Diphtheria toxin, in so far as it affects the nervous system, may likewise travel along the nerves, for it is a well-known clinical fact that the nerves most frequently paralyzed are those situated in the neighborhood of the local lesion. The virus of hydrophobia, and of acute anterior poliomyelitis, also progress along the nerve trunks.

Potent toxins can be extracted from the bodies of many bacteria which previously have been carefully killed. This was first demonstrated by Pfeiffer in the case of the cholera vibrio, and later was shown to be true also of the typhoid and colon bacilli and of other organisms. These poisons are called endotoxins because they adhere very closely to the bodies of the bacteria, and unlike the toxins of diphtheria and tetanus, are practically insoluble. They may be compared with the endoenzymes of the yeast plant. With every infection, therefore, there is an intoxication from substances produced by the bacteria, whether they form soluble toxins or not; this has recently been established in the case of dysentery.[18] It is probable, further, that insoluble toxins may provoke the formation of antitoxins[19] (anti-endotoxins) just as do those of diphtheria and tetanus, though this view is not generally accepted.[20]

The infecting organisms may do harm in still other ways, as when in a general bacteræmia they plug the smaller blood-vessels of important organs. We have learned in recent years that blood infections are by no means uncommon. Bacteria may be cultivated from the blood of most typhoid fever patients, and from no small proportion of patients with pneumonia, erysipelas and other diseases. We have come, therefore, to regard bacteræmias with less apprehension than formerly.

Many pathogenic organisms produce toxins that will dissolve red blood-corpuscles, as was first shown by Ehrlich for the tetanus bacillus.

The **resistance of the individual**, finally, is of great significance in determining whether infection shall occur and what character it shall exhibit. The pre-bacteriological era laid great emphasis upon exposure to cold, over-exertion, poor nutrition and trauma as the direct causes of disease; to-day, even though we recognize them merely as predisposing causes, we probably pay too little attention to them. Certain organisms, such as those of anthrax, plague and glanders, are so intensely virulent that they need no such predisposing factors to pave the way for them; but with the majority of bacteria some such favoring influence seems necessary unless the infective agent is present in overwhelming numbers. It is possible that the bacteria themselves produce substances that enable them to gain a foothold. In typhoid epidemics due to contaminated milk, the latter acts not

only as a vehicle, but also as an excellent culture medium in which the bacilli may grow and throw out their metabolic products.

It cannot be doubted that chilling of the body predisposes to tonsillitis, bronchitis and pneumonia, though how it does this is not known, despite the many attempts made to solve the problem.[21] Of the various explanations offered, such as lowering of the body temperature, circulatory disorders and injuries to the cells, none has been definitely established. Possibly the action of cold is to inhibit the formation of bacteriolytic amboceptors. Fatigue and inanition also lower the individual's resistance in some undetermined way. And, finally, trauma and alcoholic intoxication[22] have been shown, both clinically and experimentally, to render the individual more susceptible to infection.

Mixed and Secondary Infections.—In a number of infectious diseases, more than one variety of micro-organism is found; streptococci are often present in diphtheria, and the pus-cocci in tetanus. This is spoken of as a mixed infection. This symbiotic growth may either increase or diminish the virulence of one of the organisms. For example, isolated tetanus spores injected into the tissues of susceptible animals produce the disease only when in association with other bacteria. The latter seem to prepare the way by causing a necrosis of the tissues; for an aseptic mechanical injury will do the same. The converse —a diminution of the virulence of one organism caused by the presence of another—has not been positively demonstrated. Were this not a possibility, however, it would be difficult to explain the comparative infrequency of tetanus in view of the wide distribution of the bacillus and the marked susceptibility of man. The cultural antagonism of bacteria is more an inhibition of growth by soluble bacterial metabolic products than an actual destruction.[23]

We speak of a secondary infection when a second, or even a third, infection is superimposed upon the primary one. Secondary infections occur most frequently in those diseases which damage the skin or mucous membranes, thereby inviting the entrance of whatever bacteria that may happen to be present there. The secondary infections with streptococci, such as may develop in the course of scarlet fever, smallpox or dysentery, are especially feared. They often change the clinical picture completely; the fever takes on a different type, and various compli-

cations develop such as otitis, arthritis or endocarditis. Not infrequently the secondary infection dominates the scene and becomes the immediate cause of death. This is well illustrated in cases of septic diphtheria or scarlatina, in which the streptococcus infection provokes the fatal issue. An appropriate therapy will take into account both the primary disease and the secondary infection.

Varieties of Immunity.—Even after bacteria have succeeded in passing the protective barriers at the surfaces, there is considerable evidence to show that there exists a marked individual variation in the ability to resist infection. Of the many exposed to a disease, only certain individuals contract it, although we may be certain that many others have received the pathogenic bacteria into their bodies. Certain bacteria may be very pathogenic for one species of animals and almost without effect on another closely related species. Indeed the resistance of the same individual varies under different conditions.

These facts lead us to believe that the animal body has the power to render pathogenic organisms innocuous, even after they have entered the body, and before they have done any harm. This phenomenon is called immunity, which, in turn, may be **natural or acquired.** The former is natural to the individual; the latter has been acquired either naturally by having passed through the disease in question, or artificially by some method of inoculation.

There are two general methods of producing an **artificial immunity.** In the first, the causative organism, or some material derived from it, is injected into the individual to be immunized. The latter then passes through a sickness with a febrile reaction, etc., following which he becomes more or less immune to future infections with the same organism. This is the active type of artificially acquired immunity, because it is gained by the individual's having had the disease in a more or less modified form. In establishing this form of immunity, the material used is either injected in very small amounts, or its virulence is attenuated, so that a mild type of the disease will be produced. The immunity following such procedures develops gradually, but it is very durable, and, even though antibodies are withdrawn from the blood by venesection, new ones are formed. As examples of active artificial immunization, we may mention Wright's antityphoid inoculations, the Pasteur

treatment of rabies and the antitoxic immunity against anthrax acquired by animals after injections of attenuated anthrax bacilli.

The second form of artificial immunity—**passive immunity**—is produced by the injection of antibodies formed in the blood of another animal. For this purpose, it is customary to use the blood-serum of animals that have already acquired an active immunity to the disease in question. Passive acquired immunity develops immediately after the injection, but it soon disappears, usually in the course of a few weeks, probably because antibodies produced in another animal are in the nature of foreign substances, and as such are rapidly eliminated. Precipitins may also play a part in this elimination.[24] It is perhaps due to the close relationship of these antibodies to the normal proteids of the plasma that the former are able to exist at all in an alien blood.

The disadvantages, therefore, of an active immunity are first that the animal organism must pass through a given disease, and secondly, that protection is delayed for at least ten days. The weakness of the passive form is its short duration. To offset these drawbacks, recourse has been taken to active-passive immunization, in which attenuated bacteria, or their products, plus an immune serum, are injected together or separately.[25] But one must bear in mind, in connection with this modification, that the greater the bulk of serum injected, the fewer are the antibodies formed.[26] Besredka has obviated this difficulty by employing only the amount of serum that the bacteria can bind, removing the excess by centrifugation and washing. This method produces an immunity in twenty-four to ninety-six hours, which persists for months.[27]

The Factors Concerned in Immunity. (a) General Considerations.—Bacterial poisons stimulate the production in the body of substances capable of entering into a kind of combination with these poisons, and thus rendering them harmless. We call these substances antitoxins. When the defenses of the body against microbic infection are strengthened by an increased formation of these immune bodies, the animals thereby become insusceptible to the disease in question, irrespective of the employment of any other means calculated to increase their resistance.

The natural ability to resist bacteria is assumed to be augmented in part by an increase of bactericidal substances in the

blood—a leucocytosis perhaps representing the intermediate step, in that these substances are supposed to be the products of the white cells. It is true that many of the phenomena of immunity are associated with a leucocytosis; and, indeed, a blood rich in white cells is supposed to be more strongly bactericidal than one with few leucocytes.[28]

The invading organisms are destroyed, therefore, in the immune bodies before they can produce morbid changes. This destruction must occur rapidly if the host is to suffer no injury, because bacterial activity is itself rapid. The actual cause of the death of micro-organisms would seem, in many cases, to reside in unfavorable conditions for their growth, such as the composition of the tissues which they have invaded, and perhaps also the body temperature of the host. (The matter of the oxygen tension of the tissues would seem to be an important factor in this connection. The streptococcus, for example, when grown under different oxygen conditions, exhibits variable characteristics, not only in its cultural behavior and its morphology, but also in the experimental lesions which it produces.[29]—Ed.)

Mycotic growth *in vitro* is influenced by the character of the salts present in the media and by their osmotic tension. These considerations scarcely apply to the living host, however, as the animal body is unceasing in its effort to keep osmotic conditions constant.

More important, in our opinion, in their influence on bacterial life are variations in the proteids of the lymph and blood. The blood-serum is often endowed with bactericidal and antitoxic properties, whereby bacteria are disintegrated, either at once, or after preliminary agglutination. That this is not merely the action of an alien medium upon the micro-organisms is shown by the fact that this bactericidal power is lost if the serum be heated for thirty minutes at 55° C., a temperature which does not produce changes in the proteids. As enzymic activity is also frequently subject to similar conditions, it is not unnatural to assume that the bactericidal properties of sera are comparable in a way to ferment action, and are, therefore, attributes of the serum proteids. The nature of the bactericidal substances will be more fully considered in another place.

Also important in the part played by the bactericidal power of

the blood is the question whether the lymph and other tissue-juices are similarly endowed. As a matter of fact, the latter do contain bactericidal substances, though it is questionable whether they are comparable to those of the serum.

The bactericidal property of the body fluids does not necessarily go *pari passu* with the degree of immunity present. White rats, for example, are insusceptible to anthrax, yet their serum readily destroys the anthrax bacillus; while the blood of rabbits, which are highly susceptible to the same disease, readily destroys the organism.[30] In these instances, however, the bacteria-destroying substances differ from those just discussed, for they are inactive *in vivo;* furthermore they are not of leucocytic origin, but arise from the blood platelets in the process of coagulation; and, finally, they are not inactivated by a temperature of 56° C. Herein lies a justification of the warning of Metchnikoff not to apply unreservedly the results of experiments *in vitro* to conditions in the living organism.

The problems of acquired immunity demand special consideration. This type is characteristically seen after recovery from certain diseases, the acute exanthems being most constant in this respect. Other diseases, such as typhoid fever, generally render the individual immune for many years, or even permanently. Diphtheria and cholera, on the contrary, confer a briefer protection; while in still others, such as erysipelas, after a short immunity the predisposition to another attack is actually increased. The degree of immunity does not run parallel with the severity of the disease which produced it; in certain individuals, indeed, a very mild infection may cause a high degree of protection.

We are in no position to interpret immunity phenomena in the acute exanthems, because the causative organisms are not known. It is not unlikely, however, that in conditions such as typhoid fever and cholera, to which certain individuals are naturally immune, the inherited bactericidal power is appreciably reinforced by active immunization. This reinforcement is specific, extending only to the micro-organisms which have brought about the immune state. The serum of typhoid convalescents, for example, is highly bactericidal to typhoid bacilli, and only in a lesser degree to organisms closely related to the latter.

The study of these problems has illuminated in a most extra-

ordinary way many fundamental processes, of which only the most important can be touched upon here.

First in importance, is the ability of the blood-serum to inhibit the chemical action of certain alien substances and to destroy unicellular organisms of all types and also individual cells of more complex life. Herein lies the power of the higher animals to protect themselves against the toxins and bacteria which have passed the barriers at the body surfaces. Nor does this process of bacteriolysis set free the toxic materials contained in the bacterial bodies, for the resulting split-products of the latter are non-toxic.[31]

(b) **Complement and Amboceptor.**—Two bodies take part in the destruction and lysis of alien cells. Of these, one is of the nature of an enzyme; and the reaction and osmotic tension of normal serum and a suitable temperature are essential to its action. Kept at 56° C. for thirty minutes or cooled at 0°, it is inactivated; while at body temperature, it is most potent. This substance is constantly present in normal blood, though in variable amount; but what causes it to appear and to disappear is not known. This body has been variously called alexin (Buchner), complement (Ehrlich) and cytase (Metchnikoff). Obviously there are many different alexins, in view of their differing behavior, and also of the similarity of their action upon diverse micro-organisms. The controversy over the question of the unity or multiplicity of these substances is still active (*cf.* Hæmolysis). Metchnikoff distinguishes between macrocytases, the ferment of the macrophages (large lymphocytes) and microcytases, formed by the microphages (polynuclears). We are of the opinion of Ehrlich that there are many complements, in view of studies showing that these bodies may lose one type of activity and still exhibit one or more other types.

Complement, *per se,* is probably inactive both in immunized and non-immunized animals. The source of complement is generally attributed to the leucocytes, though whether it arises through destruction or injury of the white cells (phagolysis), or represents the secretion of the living cells, is unsettled. Fluids rich in leucocytes generally exhibit a strong alexin action, hence Metchnikoff's view that the type of white cells is a factor.[32] The composition of complement will be considered under "Hæmolysis" (p. 168).

The other substance essential to complement activity is generally resistant to temperatures over 60°. If present in normal serum, its amount is insignificant. It increases enormously, however, if the blood has been subjected to certain preliminary preparations, or the individual has passed through a disease. Immunization is synonymous with an increase in the second body, complement remaining unaltered. Various names have also been given to this substance—immune body (Pfeiffer), substance sensibilitatrice (Bordet), preparator (Gruber), fixateur (Metchnikoff), and intermediary body or amboceptor (Ehrlich).

That complement and amboceptor are distinct bodies is evidenced by their differing behavior to heat, as already noted. Thus, serum containing both, if heated to 56° C., becomes inactive, but if added, after heating, to normal serum (containing only complement), its activity is restored (reactivation). Activation and reactivation do not represent newly-discovered phenomena, though they were differently interpreted in the past.

Amboceptor is taken up and held by cells (bacteria) to the destruction of which it is indispensable. Upon this phenomenon rested Ehrlich's method of separating the immune bodies from the serum. The union of amboceptor and micro-organism occurs even at temperatures only slightly above 0° C., hence quite excluding the possibility of complement activity.

The intermediary body has a specific affinity for the cells which it attacks. The property of a serum to act upon different bacteria, and upon cells of higher organisms, resides in the possession of different immune bodies, each the product of a specific process. This specificity is the fundament of immunity, and will be discussed in that connection.

(c) **The Side-Chain Theory.**—We come now to the consideration of the mode of action of the amboceptor upon the cells of the animal organism, and of its relationship to complement. The very multiplicity of names speaks for the divergence of opinion as to the behavior of the immune bodies. Gruber and Metchnikoff attribute to the latter merely the function of enabling complement to act upon the cells. Bordet compares its action with that of a mordant; while Ehrlich looks upon it as an intermediate substance which links complement to the cells.

Ehrlich's views are based upon stereochemical con-

siderations. Complement possesses no atom-groups by means of which it can unite with those of the cells; amboceptor, however, is endowed with such haptophore groups. In addition, and by virtue of similar groups, amboceptor is complementophile. The avidity of the intermediary body is greater for the cell than for complement, hence the union with the former occurs first. This phenomenon makes possible the extraction from the serum of specific amboceptors.

How is this specific affinity of amboceptor for certain cells to be explained? If proteid-like substances gain entrance to the body, some are quickly eliminated, obviously because they are taken up by cells. As this robs them of their identity, or, in the case of toxins, renders them non-toxic, it must be assumed that they combine with some peripheral atom of the cellular protoplasm. Ehrlich conceives of these protoplasmic atoms as "side-chains" of the large proteid molecule, each cellular proteid having numerous and diverse side-chains. The alien substance is held if an appropriate side-chain is present. This is evident in tissues which have been functionally injured by the alien body; and upon this local phenomenon the theory of Ehrlich was originally founded. To-day, however, the process is no longer considered purely a local one; for amboceptor formation and alien cell fixation are thought to occur also in tissues not so injured.

It is a characteristic of the living cell to react to the stimulus produced by the union of side-chains in amount far out of proportion to the demand. The excess are cast off and circulate in the blood as antibodies. The degree of new formation of chains depends essentially upon the character and intensity of the stimulus; thus the cells may be so injured by an especially severe infection as to be rendered incapable of producing immune bodies.

The vulnerable point in the side-chain theory, in our opinion, is that relating to the production of new chains by the injured molecule. This has been likened to the reaction of tissues to an irritant, a reaction which may be so pronounced that the new tissue is produced in excess. The two processes, however, are fundamentally different, for, on the one hand, we are dealing with the reaction of living tissues as a whole to an injury, while, on the

other, it is a reaction involving individual molecules. No reaction analogous to this is known to chemistry.

The Hæmolytic Action of Alien Plasmas.—The destruction of red blood-corpuscles by alien blood has become a matter of great interest in recent years, for the study of the factors concerned in the phenomenon has enormously increased our knowledge not only of physiological processes in general, but also of the principles of the bactericidal action of the blood-serum.[33]

That the blood of a given animal can dissolve out the hæmoglobin of the erythrocytes of another species has long been known. Certain animals are particularly sensitive in this respect and some sera are especially toxic. To a certain degree, indeed, the mutual interaction of the sera of different animals is constant; yet enormous individual variations occur, and sera are known which produce hæmolysis even in animals of the same species.[34] As hypotonic salt solutions likewise cause laking, it is natural to ask whether hæmolysis is merely the effect produced by a serum of different osmotic tension.[35] Morphologically, indeed, red cells subjected to the action of an alien blood, on the one hand, and to a hypotonic salt solution on the other, are much alike.

Other investigators see in hæmolysis a process similar to that just discussed in connection with bacterial destruction, *i.e.*, based upon the action of a complement plus an amboceptor. The complement in this case is also unable to withstand a temperature of 56° C., and is inactive without the intermediate action of another body even in the normal destruction of red cells. Dog serum, for example, heated to 56° is no longer hæmolytic, but if to it be added fresh guinea-pig serum, *per se* inactive, the hæmolyzing power is restored. This experiment indicates incidentally that amboceptor is present in normal dog serum. By a process of dialysis, complement (guinea-pig serum) can be shown to consist of two simpler bodies, the so-called mid-piece and end-piece, which differ physically and chemically.[36]

The hæmolytic action of a serum may be intensified if the animal (A) from which it is derived be first injected over a long period with the red cells of the animal of the other species (B).[37] The essential element provoking the hæmolytic power is the stromata of the red cells of B, irrespective of whether the serum of

A was hæmolytic for B before the preliminary treatment. In other words, the stromata of B's cells injected into A, endow the serum of the latter with the power of dissolving out the hæmoglobin of the cells of the former. The hæmolytic action is specifically confined to the red cells of the species used in the experiment.

Immune (hæmolytic) serum, like normal serum, is inactivated by a temperature of 56°, and reactivated by the addition of fresh serum from an untreated animal.

There are additional points of analogy to the process of bacterial immunization. Thus, essential to the hæmolytic power of the body destroyed at 56° is the action of another which may be heated to 60° with impunity; and further, this second body tends to multiply. Unlike complement, it is specific, being fixed only by those red cells marked for hæmolysis. The amboceptor concerned in hæmolysis may be isolated in a manner similar to that described for the bacterial immune body (see p. 167).

As a given serum is able on the one hand to dissolve red cells of diverse animals, and, on the other, after being heated to 56°, is susceptible of reactivation by the addition of various complements, it is natural to assume that normal blood contains diverse amboceptors and complements. In fact, both normal and immune sera may be deprived *seriatim* of specific hæmolysins. Ehrlich has shown this experimentally in the varying behavior of hæmolysins toward the red cells of the same species. We shall return to this question of multiple amboceptors, both for red cells and for bacteria, particularly because in a physiological way it is difficult of conception.

Recent studies[38] indicate that in the hæmolytic process, a lipoid envelope, or a union of lipoids and proteids in the red cells, undergoes disintegration, and that the antigen of artificially produced hæmolysis is a lipoid body. This conception is even more probable in the case of substances from the red cells which inhibit hæmolysis *in vitro*. Complement also is supposed to contain lipoids.[39] A definite conclusion, however, as to the significance in hæmolysis of these fat-like bodies is not yet warranted. Meyer[40] disputes the part played by lipoids, because they are insoluble in the ordinary fat solvents, and even in specific lipoid solvents.

Antitoxins.—In the matter of the immunity gained by the animal body to toxins in general, we shall confine ourselves to

the fact that bacterial poisons are robbed of their toxicity by certain constituents of the serum. For this discovery we are indebted to v. Behring, who found that the blood of animals inoculated with the diphtheria bacillus, rendered innocuous the toxin of this organism.

A considerable number of chemical substances of diverse origin and closely related to the enzymes are altered by bodies which they encounter in certain sera. That actual destruction of the poisons does not occur is shown by the fact that they may still be demonstrated after the antitoxic action. What actually occurs is a fixation of the toxin by the antitoxin. This would indicate that the reaction is one of colloids,[41] at least in the case of antitoxin, which is always combined with a proteid.

The source of antitoxin is variously ascribed. Buchner originally contended that it arose within the body through alterations in the toxin, thus explaining its essential specificity. It is our opinion that antitoxin is the reaction product of the organism to the poison. Behring's famous formula reads: In the living organism a given substance, which, if present in the cells means poisoning, occurring in the blood itself promotes recovery.

To discuss certain factors pertinent to the question of antitoxins would be repetition. Thus, Ehrlich's conception of antibody formation is based on that of antitoxin production. The principles of the side-chain theory apply equally well to the process of toxin fixation, and to the conception of immoderate over-production of side-chains, which, cast into the circulation, represent the individual's immunity to the poison in question.

Antitoxin formation is not confined to those cells which clinically have been subjected to the action of the poison, but is the product of all cells with suitable side-chains. This is a further evidence of the comprehensiveness of the Ehrlich theory. The hen and the alligator are highly insensitive to tetanus, yet they readily produce tetanus antitoxin; in other words, tissues other than nervous possess the appropriate receptors. Again, tetanus toxin remains inert for a long time in the blood of the turtle, and yet no antitoxin is formed, because suitable side-chains are not present. Hence, tetanus occurs only when the central nervous system can fix the toxin.

Once the stimulation to antitoxin formation is initiated, antibodies continue to be produced for a long period. For this reason, the immunity acquired by passing through a disease is more or less durable, and for the same reason, the blood of animals strongly immunized may be repeatedly withdrawn, and yet that which is left will always develop new antitoxin. Similarly the injection of pilocarpin will increase the amount of antitoxin in the blood, probably because it stimulates the cells to secrete.

Remarkable it is, however, that antibodies—this applies less to antitoxins than to other immune bodies—can persist in the blood. No other explanation seems possible than that their molecular construction is altered and that they become, in fact, normal constituents of the blood, endowed with the properties of its proteids. This would explain both their permanence and their chemical action.[42]

Antitoxin is constant and abundant only in the blood of animals which have passed through a disease or have been artificially immunized to that disease. Yet it may be present in the serum of healthy individuals, and even in the blood of the new-born. This remarkable fact is explainable in accordance with the Ehrlich hypothesis on the assumption that for some reason the side-chains for which the toxin has an affinity have been cast loose into the circulation.

Antitoxins multiply exclusively, or at least most energetically, in response to the toxins which have stimulated their production. They are less resistant than toxins to light and oxygen, and are injured by a moist heat of 60°–70° C. In experimental immunization, the antitoxin content of the blood begins to increase with the fifth day—the maximum for diphtheria occurring on the tenth day and for tetanus on the seventeenth. Thereupon occurs a decline which reaches a stationary level in about two weeks and is maintained for some time. Antitoxin is present not only in the blood, but to some extent in all the body fluids, even in the milk.[43]

Precipitation and Precipitins.—Just as microbic poisons are rendered harmless by normal, and particularly by immune, sera, so any type of proteid (in clear solution) may be precipitated by blood artificially inoculated with the same material. The bodies calling forth this reaction are known as precipitins.[44] The

proteid substances (antigens) employed in this type of immunization are called *precipitinogens* and the resulting product a *precipitate*. Most precipitinogens are proteids alien to the animal injected, isoprecipitins rarely being formed. These precipitins cannot be separated from the globulins of the blood.

An acid reaction, especially if due to organic acids, is most favorable to precipitation, and salts, irrespective of their nature, are essential. An excess of precipitinogen prevents the reaction (so-called *specific inhibition*).[45] Inhibition is spoken of as *non-specific* if an alien proteid solution of high concentration retards the appearance of the precipitate, or holds it in suspension. For these reasons, the phenomenon is regarded as a *colloidal reaction*; and as precipitinogen and precipitin are used up in the process, there can be no question of an enzymic action.

Precipitins are relatively resistant to certain influences, as, for instance, to a long-continued temperature over 60° C., to desiccation and even to putrefaction. They cause precipitates not only with their specific precipitinogens, but also, though less actively, with related proteids. The more closely related a given proteid is to the body employed in immunization, the more pronounced is the precipitate. Upon this basis rests the employment of the reaction in the problems of evolution. *Only in a quantitative way, therefore, may the reaction be regarded as specific.*

Furthermore, the precipitins of an immune serum cause precipitation with other proteids of the organism which furnished the original precipitinogen; thus, the serum of an animal immunized with human blood, precipitates human sperm, human milk, etc. Ehrlich looks upon precipitins as side chains comparable in general with antitoxins and bacterial antibodies.

The precipitin reaction has already found a considerable practical application and with further development will undoubtedly prove of great value in differential diagnosis. In the infectious diseases, the proteids of bacterial metabolism—the precipitinogens—may be found in the blood and tissues; and at a later period, the corresponding precipitins. It is not necessary to know the organism itself to identify these two bodies. Attempts have also been made to adapt the reaction to the diagnosis of carcinoma;

further, to demonstrate that the substances responsible for puerperal eclampsia are of fetal origin; and finally, to isolate the toxic proteid of bothriocephalus infection, and to establish that the albumin in nephritic urine comes from the body proteid itself.

In medical jurisprudence the precipitation reaction has proved of great assistance, particularly in determining whether a given specimen of blood is from man or not. Uhlenhuth's[46] method of immunization with proteids of allied species, *e.g.*, man and ape, facilitates the diagnosis between the blood of these two. The precipitin reaction persists in material which has been exposed to desiccation for as long as seventy years, or which has been frozen, or exposed to sunlight or moderately decomposed.

Complement Fixation. The Wassermann Reaction.—Still another advance, eventuating in the combination of the precipitation and the hæmolysis reactions, followed the discovery by Bordet and Gengou[47] that the bringing together of red corpuscles or bacteria with their specific immune sera (so-called sensitization) led to the fixation of complement. In other words, each time antigen is brought into contact with its antibody, complement vanishes. The disappearance of complement, evidenced by the non-appearance of hæmolysis, is striking even in minimal precipitin reactions. To an otherwise suitable hæmolytic system, composed of red cells, amboceptor and complement, the addition of precipitinogen and its antiserum inhibits hæmolysis if complement is fixed. The proteids of human blood are sensitive in this way up to a dilution of one hundred thousand and more.[48]

Antigens and their antibodies may also, as already noted, be demonstrated in the case of micro-organisms not susceptible of cultivation, or where we have to do with unknown viruses, for they are present in extracts of definitely diseased organs, and late in the process in the serum of the affected individual, and also in the serum of animals immunized with the organ extracts. The evidence of the presence of antigen and antibody in a hæmolytic system is the inhibition of hæmolysis. This phenomenon enables one, by varying the experimental conditions, to demonstrate in a given serum, or inflammatory fluid, the presence of antigen in the early stages of a disease, and of antibody in the later stages, or whether the disease is actually infectious or not.[49]

Wassermann and his co-workers, on the basis of these reactions, have evolved a **serum reaction for syphilis.** It was at first believed that the bringing together of syphilitic antigen (extract of the fetal luetic liver) and antibody (luetic serum) was essential to the fixation of complement and the consequent inhibition of hæmolysis when red cells with their specific amboceptors were added. Further study, however, revealed the astonishing fact that extracts of luetic organs were by no means necessary and that alcoholic extracts of normal organs sufficed. Complement fixation, therefore, occurs as a consequence not of the meeting of luetic antigen and luetic antibody, but as the result of the contact of a normal body substance with luetic serum. These substitutes for antigen, being soluble in alcohol, are probably lipoids.

An entirely satisfactory explanation of the Wassermann reaction is, for the present, wanting. This does not detract, however, from its great practical value.[50] Many observers insist on the use of syphilitic antigen in order to obtain the most dependable results. If extracts of normal organs (heart-muscle) are employed, great care must be exercised in keeping them of uniform composition.

(The principle of complement fixation has been adapted to the diagnosis of other conditions, though with results far less satisfactory and constant than in the case of syphilis. In certain types of gonorrhœa[51] and in echinococcus disease,[52] the reaction has proved of considerable practical value; in tuberculosis,[53] typhoid fever and other diseases, it has generally been discarded. Gonorrhœal complement fixation, unlike that occurring in syphilis, is a biologically specific antigen-antibody interaction.—Ed.)

Agglutination and Agglutinins.—The phenomenon of agglutination is a further type of reaction exerted by the blood-serum upon alien cells and bacteria. It is manifested by a clumping and precipitation of the latter.[54] The relation of agglutination to the process of immunity is still not clear. The fact that the agglutinins are less sensitive to heat than are immune bodies is scarcely a distinguishing mark, for the latter are themselves not constant in this respect. Though the agglutinating property of a serum is largely independent of its bactericidal power, yet it appears that agglutination has some influence upon the destruction of the

clumped cells. Nevertheless agglutinated bacteria may live a long time, and, furthermore, dead bacteria will also clump.

The current interpretation of the nature of agglutination is that a portion of the bacterial substance (the agglutinogen) is bound by the antibody (agglutinin) which it gives rise to. This is also in all probability a reaction of colloids. The agglutinins are combined in a few minutes,[55] but hours may elapse, especially at low temperatures, before agglutination is distinctly manifested. Centrifugation noticeably hastens the precipitate.[56] In the Ehrlich theory, agglutinins are analogous to precipitins, antitoxins, hæmolysins, etc. Temperatures over 70° C. are necessary to destroy them; and they resist desiccation, to a certain degree light, and even decomposition, but they are inactive in solutions not containing salts.

Normal serum is only feebly agglutinating, dilutions of 1 : 50 generally inhibiting the phenomenon. Immune sera, on the contrary, are powerfully agglutinative, dilutions of even 1 : 100,000 clumping typhoid bacilli. Quantitatively, therefore, agglutination, like precipitation, is specific; for although closely related micro-organisms may also be agglutinated (group agglutinins) by a specific serum, this occurs only in comparatively low dilutions. The higher dilutions act only on the specific micro-organisms that caused the infection. Agglutinins may also be found in insignificant amounts in extracts of organs freed from their blood, and in milk, pus, etc.

The agglutinins appear in the blood of warm-blooded animals in from three to ten days after the inoculation of bacteria or their products. They increase rapidly in amount for about a week, and then diminish more or less gradually. As a rule, the typhoid agglutinins disappear from the blood of man after about one year, though there are many exceptions to this rule.

(In this connection may be mentioned the method of vaccination against typhoid introduced by Wright.[57] The vaccine is obtained from a bouillon or agar culture of the bacilli, killed at a temperature of 54° to 55° C. Three injections are made at intervals of ten days, the first of five hundred million of the bacteria, the last two of one billion each. The injections usually produce a mild local reaction, and variably severe constitutional symptoms of fever, headache, malaise, etc. Immunity

is granted by an increase in the agglutinating and bactericidal powers of the blood. The duration of the Widal reaction after vaccination is as yet undetermined; at any rate, in cases suggestive of typhoid, a previous vaccination must be taken into account when the agglutinating power of the suspected serum is being determined.

Statistics based upon vaccination in the British and American armies[58] indicate that protection against typhoid is granted in the vast majority of cases. How long this immunity endures has not been definitely established; it would seem, however, that revaccination every four years is quite sufficient.—ED.)

The Relation of Antitoxins and Bacteriolysins to Immunity.—Observers, generally, have attributed the state of immunity produced by spontaneous and experimental infection with organisms not known to form soluble toxins, to the appearance of bactericidal substances in the blood. Investigation has shown, however, that the blood-serum becomes bactericidal before the disease has run its course—in typhoid, for example, at a time when immunization could not possibly have been established; and furthermore, that the same serum is less bactericidal in cultural studies than when employed in the living animals.[59] These facts indicate that the power of destroying micro-organisms is not the only element in the acquisition of immunity.

In diseases due to bacteria producing a soluble toxin, the formation of antitoxin is, without doubt, one of the chief factors in recovery—hence, the adaptation of antitoxin immediately after its discovery both to the prevention and the cure of diphtheria. Recovery is possible only if toxin already anchored is rendered harmless by the antitoxin introduced. It soon became apparent, however, that to cure, considerably more antitoxin was needed than to immunize, and that the longer the disease had been in progress, the more antitoxin was called for, so that at a certain point even enormous doses were unavailing.[60] In the practical application of serum therapy, a knowledge of these factors is indispensable. Large doses of serum, therefore, are indicated, and of a concentration as high as possible to obviate the effects of large amounts of an alien proteid.

Ehrlich introduced a method of standardization of the different immune sera. In the case of diphtheria

antitoxin, for instance, the immunizing unit was contained in a serum one cubic centimetre of which neutralized toxin equivalent to one hundred times the lethal dose for the guinea-pig. But as the standard toxin solutions were not stable, this method has not continued in use, and, at present, sera are controlled with a standard immune serum in powdered condition and protected from the light and air, in the Ehrlich Institute.

The curative value of diphtheria antitoxin as against living Klebs-Loeffler bacilli, according to some observers, does not run parallel with its antitoxic titer. It is possible that the avidity with which toxin and antitoxin combine is also a factor, and that a serum of high potency may display only a slight avidity of this sort.[61] This conception, however, is vigorously attacked by those who say that the therapeutic value of a serum depends upon the number of immunizing units it contains.[62]

Antitoxic sera disappear rapidly from the circulation (see p. 162). In diphtheria epidemics, therefore, the indication is to repeat the prophylactic dose; yet the danger of anaphylaxis must be considered (see below).

(B. Schick[63] has suggested a method for determining whether an individual exposed to diphtheria is in need of prophylactic injections of the serum, in this way obviating the promiscuous use of the latter and the dangers of anaphylaxis when the disease has actually developed. This method, which is based upon the existence of some degree of natural immunity in the individual, consists of the intracutaneous injection of an exceedingly small fixed dose of diphtheria toxin. If the serum of the person who has been exposed contains no antibodies, a local inflammatory reaction occurs, and antitoxin is indicated.—Ed.)

Injected subcutaneously, antitoxin is slowly absorbed, the blood not attaining its maximum concentration until after the third day. The advantage of the intramuscular method resides in the fact that absorption is well advanced within the first twenty-four hours. The most rapid results follow intravenous injection.[64] In meningococcus meningitis the serum must be brought into direct contact with the micro-organisms. It would seem that the tendency has been to employ antitoxin in too small doses, especially when sufficient time has elapsed to have allowed

toxin to become anchored to the cells. In recent years, indeed, heavier doses have been the rule.[65]

In the therapeutic application of the principles of immunity, attempts were made, even at an early period, to create an active immunity both during the incubation period of a disease and during its early course. The Pasteur treatment in rabies is an example. Later, efforts were made to cure typhoid fever by injections of killed bacilli. (The results both with the method of active immunization and with injections of typhoid immune sera have been generally unsatisfactory; at any rate, far less encouraging than those obtained by prophylactic vaccination against typhoid fever. The sensitized virus-vaccine of Besredka seems to offer a more encouraging outlook.—Ed.) In chronic infections the indication for vaccine and serum therapy is clearer. (Vaccines and immune sera have proved highly efficacious in certain well-chosen chronic conditions; but their promiscuous use and their commercialization have brought this method of active immunization into more or less disrepute, so that to-day it is much less employed than formerly.—Ed.) The introduction of tuberculin by Koch also led to the extensive application to tuberculosis of this mode of treatment. The so-called opsonic therapy of Wright (see p. 189) is based upon similar principles. The rapid and enduring immunity given by the combined active-passive method with extremely small doses of sera has led to its therapeutic adaptation,[66] in puerperal septicæmia among other conditions.

Anaphylaxis. Serum Disease.—In all types of immunization the tissues build reactive substances more rapidly and abundantly when antigen is repeatedly injected. The cells thereby become endowed with an altered power of reaction, by v. Pirquet, who first recognized the practical significance of the phenomenon, termed allergie; instead of immune, they become hypersensitive. This was observed by v. Behring in horses, which succumbed to a relatively small dose of toxin, though their blood contained abundant antitoxin. The Ehrlich theory would explain this paradox on the assumption that side-chains held closely by the tissue-cells possess a greater affinity for toxin than does antitoxin—the chains free in the blood.

Allergie is exhibited more regularly after the parenteral introduction of alien proteids than after toxin injection. This type of hypersensitiveness, known as anaphylaxis, after Richet,[67]

must be reckoned with as an unwelcome by-effect both in active and passive immunization. Untiring research speedily established this apparently enigmatic process on a firm basis.[68] Friedberger, indeed, has recently demonstrated anaphylatoxin *in vitro*.

The fundamental experiment best suited to demonstrate the phenomenon is the following: A guinea-pig is injected subcutaneously with a foreign proteid, *e.g.*, one milligram of normal sheep serum. This injection represents the preparation or sensitization. In ten days, five milligrams of the same serum are given intravenously—the reinjection. The animal at once becomes restless, has severe convulsions and within five minutes dies in asphyxia. The characteristic manifestations are dyspnœa, paralysis of the peripheral vasomotor apparatus—hence a marked fall in blood-pressure—leucopænia, even to the absence of the polynuclears, a fall in temperature as great at times as 10° C., spasm of the bronchial muscles and a consequent pronounced pulmonary emphysema, a diminished coagulability of the blood, and a reduction of complement in the serum.

An intraperitoneal reinjection produces the same symptom-complex, except that the duration is prolonged and death is not inevitable. If the second injection be subcutaneous and not too large, there appears locally an œdema which quickly becomes hemorrhagic and ends in sluggish ulcers (Arthus). By the intravenous route, sensitization may be produced and reinjection made with infinitesimally small amounts of sheep serum—for the former, the one five-thousandth part of the fatal intravenous dose, and for the latter, the one one-thousandth.

An incubation period of about ten days must be allowed to elapse between the first and second injections—a fact allying anaphylaxis with the phenomena of infection and immunity. The allergic state may continue for a long period, in guinea-pigs up to two years (Rosenau and Anderson) and in man up to five (Curie). Man, however, is far less sensitive to reinjection than is the guinea-pig. All warm-blooded animals are more or less predisposed to anaphylaxis, while of cold-blooded, only the frog has thus far been sensitized.

The reaction occurs irrespective of the kind of alien proteid used, whether animal, vegetable or bacterial. The determining component of the serum is the euglobulin. Pointing to the

specificity of anaphylaxis is the fact that the same proteid must be used for sensitization and reinjection. Rosenau and Anderson showed that guinea-pigs could be sensitized by the oral administration of abundant proteid in the food, followed by parenteral inoculation of the same proteid. Indeed, using the proteid of the crystalline lens, rabbits were made allergic by oral introduction both in sensitization and in reinjection.

Certain non-alien proteids may also provoke anaphylaxis in a manner analogous to precipitation phenomena already noted. Guinea-pigs, for example, may be so sensitized by the proteid of the guinea-pig's lens—even by its own lens proteid—as to react typically upon reinjection of the same body. Similar results have been obtained with the spermatozoa and ova of the same species, especially when the former are injected into pregnant animals.

The transmission of allergie to the offspring is the first evidence of the hereditary nature of an apparent predisposition to a disease. Such an inherited sensitiveness lasts only about six weeks and is transmitted exclusively by the mother's serum (to the offspring).

The fact that the blood-serum of a sensitized animal, if introduced into another animal, renders the latter also allergic (passive anaphylaxis) points convincingly to the immunologic character of anaphylaxis.

Serum disease, a special type of anaphylaxis which we shall consider in another place, is ascribed by v. Pirquet to the meeting of an alien proteid with its specific antibody. It would carry us too far afield to review the various theories adduced in explanation of the anaphylactic reaction. That of Nicolle,[69] which seems to explain the phenomena of immunity in general, merits special consideration. According to this theory, there are two classes of antibodies formed, coagulins and lysins, the former embracing antitoxins, precipitins and agglutinins, the latter perhaps all lytic antibodies which together with complement render accessible the actual poison in antigen. If the latter is reinjected into the immune organism, it is held by the coagulin and destroyed by the lysins. If these last, however, prematurely grasp antigen, then, with the aid of complement, toxin is quickly set free. On this assumption Nicolle was able to demonstrate that the serum of anaphylactized animals, together with the antigen

employed, led to fixation of complement (diphtheria toxin with the serum of animals sensitized with the same toxin).

Friedberger has succeeded in isolating anaphylatoxin starting with these premises, *viz.*, first, that unprepared animals may be made anaphylactic by receiving a mixture of sensitized serum plus the specific antigen; and, secondly, that complement is essential to the formation of the anaphylactic poison. His method was as follows: Horse serum (antigen) was mixed with its antibody (rabbit serum sensitized with horse serum) and to the resulting precipitate—first carefully washed with physiological salt solution—was added complement (fresh guinea-pig serum). The precipitate occurring here was removed by centrifugation. The supernatant guinea-pig serum produced in animals (not previously sensitized) classical anaphylactic shock, and must, therefore, have contained the anaphylactic poison. One milligram of an alien serum was sufficient to call forth an active anaphylatoxin; in the production of the latter, therefore, not the amount but rather the number of antibodies is important. If the latter are over-abundant, the proteid molecules disintegrate too rapidly, while the toxic intermediary products are transformed into simpler, innocuous substances. The same is true when the antibody action is too prolonged.

Anaphylaxis, therefore, is an antibody reaction and as such must be identified with other immunity phenomena. Antiproteins, then, would properly be classed with the amboceptors, though they are not to be identified with the bacteriolytic amboceptor. Bacteriolysis indeed interferes with anaphylatoxin formation. Normal serum, among the other antibodies it contains, also contains one in small amount which can split proteid in the presence of complement and which is increased enormously if the specific antigen be injected.

A foreign proteid after the first injection is slowly disintegrated; after the second, when antibodies are abundantly present, the latter and the alien proteid are brought into sudden contact, the proteid is rapidly split with the aid of complement, and the intermediate products—probably identical with those of intestinal digestion—exert a toxic action, in all likelihood, because they cannot be eliminated as is the case in the digestive tract. This conception of the mechanism of anaphylaxis is strengthened by the fact that certain anaphylactic manifestations are identical

with those of peptone poisoning; anatomically, too, the picture is the same.

If a sensitized animal be reinjected with a dose of foreign proteid, insufficient to cause death, antibody formation is arrested in such a manner that a third injection of the same antigen, even in large amount, and following quickly upon the second, is borne with impunity. This condition is called antianaphylaxis (see p. 185).

What is known as primary anaphylaxis may be illustrated as follows: If a normal animal receives a large dose of an alien proteid—not great enough, however, to cause death—this proteid is partially split by those antibodies normally present in the serum. Simultaneously, the injection leads to the formation of new antibodies, with the result that a certain residue of the foreign proteid, together with these antibodies, exist side by side without interaction, due apparently to some peculiar regulatory mechanism. If this serum be injected into a normal animal, however, this mechanism is ineffective, the antigen residue combines with antibody and anaphylaxis results. The practical importance of this is obvious: a serum must not be withdrawn too soon after the reinjection, as free antigen may still be present. It is advisable, furthermore, to test curative sera before distribution with this possibility in mind.

One millionth of a milligram of a protein substance injected into a sensitized guinea-pig causes fever, whereas, in a normal animal five centigrams are necessary. In this connection, we would note that several decades ago, the author[70] produced a febrile reaction with proteids of all kinds and also with their split-products, the reaction becoming more marked with the repetition of the injections. Even at that early period, the author asked himself whether substances of different thermic attributes arose only after the disintegration of the bacteria in the living organism. A more or less constant fever was produced by Friedberger and Mita, in sensitized animals, by continued parenteral injections of minimal proteid doses. Injection of larger amounts, however, at the height of the artificial fever, led to a pronounced fall in temperature and to the condition of anaphylaxis. Further, if the sensitized animal was injected with the given proteid during the incubation period, a febrile reaction took place, but with a considerably smaller dose than in normal animals. Friedberger

concludes from this that antibody formation does not take place suddenly from the seventh to the tenth day, but that it begins in the second twenty-four hours and gradually increases. This observation is of importance in the matter of the negative phase.

Local anaphylaxis does not predicate the existence of sessile receptors, but rather the local accumulation of antigen which combines with antibody free in the circulation at that particular point. On this basis, Friedberger explains pulmonary infiltration in pneumonia, pneumococci collecting in the lungs and there coming into contact with their specific antibodies. The resultant systemic manifestations are due to anaphylatoxin formation. Friedberger and Mita produced fever and aseptic inflammation in the lungs of sensitized guinea-pigs by having them inhale the specific serum. Thus the fever curve, and all of the other characteristic symptoms of different infections, may be imitated by the continued parenteral injection of a foreign, *per se* non-toxic, proteid by varying the dosage, the interval between injections and the point of injection, and by producing a variation in the number of antibodies formed and used up—or otherwise expressed, in the resultant amount of anaphylatoxin. Herein would reside the link between infection, immunity and anaphylaxis as set forth at an earlier period by Wolff-Eisner, whose conception, however, was purely hypothetical and differently formulated.

Infection from this point of view represents an attenuated and protracted anaphylaxis, the incubation period corresponding to the preparation of the animal. As long as the infection continues, a minimal parenteral proteid introduction is taking place, for the infectious agents are constantly multiplying and undergoing destruction. The analogues in the anaphylactic process would be minimal doses of artificially introduced amorphous proteid, a variably great consumption of antibodies, antianaphylaxis, local processes, fever, etc.

In the opinion of Friedberger, there is only one anaphylatoxin. The analogue of this he finds in the uniform protein split-products arising from the most diverse proteids in the course of intestinal digestion. The union of antibody with its appropriate antigen, therefore, would represent the only element of specificity in the process. He bases this conception upon the observation that by intravenous injection of proteid split-products, a symptom-complex is produced identical with that of anaphylaxis. This has

been confirmed from many sides. Biedl and Kraus had similar results with peptone. In Friedberger's mind it is unnecessary to assume that in the different infectious diseases—excluding those which give rise to soluble toxins (tetanus, diphtheria, botulism)—in addition to anaphylatoxin, there is formed another peculiarly specific poison.

In our opinion, Friedberger has gone too far in his attempt to identify the phenomena of infection with those of anaphylaxis, granting that much in the clinical picture of the former can best be interpreted on an allergic basis. Nevertheless, peculiar to each infection are many features not thereby accounted for and which postulate the assumption of a specific poison. The striking somnolence in hen cholera is a case in point, as Pasteur has shown that this same symptom may be produced without the injection of living bacilli if a bouillon filtrate of the organism—enormous in amount it is true—be introduced. Here it is not an indifferent poison that is acting, for still larger doses of the filtrate cause death. Klemperer is also of the opinion that the characteristic pictures of the different infections are to be interpreted with difficulty except on the basis of specific toxins, citing as an example the necessity of assuming the presence of the toxin of the tubercle bacillus to explain caseation. Friedberger, in reply, calls attention to the fact that reinjection of proteid in sensitized rabbits causes necrosis and caseation. Citron, on the other hand, points out that if there were but one anaphylatoxin, active immunization to one infection would necessarily mean that it existed to all.

As we have already noted, the anaphylactic state may also be produced by feeding foreign proteids. On this ground, possibly, are to be explained those urticarial conditions which follow the ingestion of a particular food. Here we must assume that as a result of abnormal intestinal permeability, due in turn perhaps to digestive disorders, proteid enters the circulation after a preliminary splitting by the intestinal ferments. This would be equivalent then to parenteral introduction, and minute amounts would suffice. Possibly, an albuminous food is not unequivocally necessary to produce this urticarial phenomenon; the specific antibody may have been previously formed, or have arisen with the first occurrence of intestinal permeability. The idiosyncrasy of certain children to cow's milk, evidenced by

fever, vomiting and diarrhœa, asthma, convulsions and collapse, is very likely anaphylactic in nature.

The so-called **serum disease**, because of its clinical bearing, is the best known and most important type of anaphylaxis. To v. Pirquet and Schick is due the credit of first calling attention to the symptom-complex. It occurs in about ten per cent. of individuals receiving for the first time an injection of an immune serum (as a rule that of immunized horses). The incubation period is roughly ten days, which represents the time required for the formation of sufficient antibodies. Accompanied by fever, there occurs an urticarial, sometimes a polymorphous exanthem, generally starting from the site of injection. The rash persists for two to three days, or longer, the lesions appearing in crops. Pain in the joints and muscles and an albuminuria may be present. Indeed, the picture of serum-sickness may differ in no respect from that of an acute infection.

It is evident from the foregoing that serum anaphylaxis occurs most frequently after the reinjection of an immune serum, when the interval between the injections is not less than ten to twelve days. With this incubation period, the symptoms begin at once (v. Pirquet's immediate reaction). Serum disease, like experimental anaphylaxis, occurs most readily after intravenous injections.

To prevent serum disease, it has been suggested that the prophylactic injection be made with an immune serum obtained from sheep or cattle, to the end that horse serum may then be employed without risk if the disease develops despite the preventive dose. In the Pasteur Institute the sera are heated at 56° C. for a number of days and are thus made less toxic. The same is true of sera which have been allowed to stand for a long period. Apparently the best method of guarding against serum disease is by first rendering the individual antianaphylactic, by introducing subcutaneously or intravenously, in high dilution, a small amount of the serum indicated, and gradually increasing the dose, until after several hours the full injection may be made (Besredka).[71] Friedberger accomplishes the same purpose by running the full dose into a vein, very slowly, consuming at least ten minutes in the process. The good results of both methods reside in the using up of anaphylactic antibodies.

To anaphylaxis, further, are ascribed the toxic manifestations

sometimes observed, when in the course of an operation, the fluid contents of an echinococcus cyst escape into the free peritoneal cavity. In this case, the individual has been prepared by the absorption of the proteid of the parasite during the course of the disease; while the shock itself is due to the peritoneal absorption, consequent to the operation. Eclampsia is also classified by some among the anaphylactic processes. The mother is assumed to be sensitized by the amniotic fluid, the onset of symptoms following a later more energetic absorption. This hypothesis seems to be borne out by the observation that guinea-pigs, sensitized with the serum of an eclamptic, exhibit anaphylactic shock after a subsequent injection of liquor amnii. Hay fever is undoubtedly an allergic manifestation. Symptoms do not appear until the second decade; during the first years of life there is taking place, by inhalation, an absorption of the foreign proteid (pollen) leading to antibody formation. Repetition of the inhalation, analogous to the reinjection of some alien proteid, calls forth the hay fever attack in the late summer. That this conception is well founded is evidenced by the fact that injections of the same pollen proteid, at any time of the year, cause hay fever. Whether the sensitization due to tuberculin belongs in this category remains to be seen; thus far, at any rate, it has not been passively conferred.

(Many local allergic manifestations are of considerable diagnostic worth.[72] Prominent among these are the different local tuberculin reactions—the v. Pirquet and the Moro percutaneous tests, the intracutaneous test of Mantoux, the ophthalmo-tuberculin reaction of Calmette and Wolff-Eisner, and the "Stichreaktion" of Escherich; further, the luetin percutaneous phenomenon of Noguchi; the gonococcus local reaction (Irons); and the ophthalmo-reaction in typhoid (Chantemesse). Essential to a proper interpretation of these reactions is an understanding not only of their value, but also of their limitations in the different types and stages of the above-mentioned conditions.

The **Abderhalden immune-ferment reaction** may properly be spoken of in this place, as it represents an outgrowth of studies directed toward the explanation of the phenomena of anaphylaxis. Observers generally agree with Vaughan that the toxic manifestations of anaphylaxis are due to the poisonous substances formed by the rapid splitting of foreign proteids. That is to say, the

process of sensitization leads to the production of ferments capable of splitting proteid when reinjected. Some of these ferments are non-specific, *i.e.*, they can disintegrate other proteids than those which stimulated their formation. Certain ferments, on the contrary, are specific for a particular proteid. Of the latter the first to be thoroughly studied was that produced in the maternal organism by the action of the chorionic epithelium (placenta). Placental extract brought into contact with the blood-serum of pregnant women is split into the simpler proteid molecules, such as the amino-acids, etc.

The technical phase of the test rests upon the principle that proteid, being a colloid, does not dialyze through appropriate membranes, but that the crystalloid split-products do pass through such membranes, after which their presence can be recognized by appropriate tests (ninhydrin).

From the adaptation of the immune-ferment reaction to the early diagnosis of pregnancy, the test has found a wide application in other morbid processes, particularly carcinoma, psycopathic conditions, tuberculosis, thyroid anomalies, etc.

Despite the vast amount of work reported in the past few years, tending to confirm the conception of Abderhalden, the specificity of the reaction has lately been seriously questioned.[73] A final judgment as to its value, therefore, must be reserved.—Ed.)

Phagocytosis and Immunity.—Wandering cells, derived partly from the white cells of the blood, and in part from the fixed tissue cells, pervade all parts of the body, carrying with them materials of diverse kinds. They appear wherever there is a foreign body —one not soluble in the tissue juices, or assimilable by the cells— and remove it. This activity is not purely mechanical, for they can also dissolve and destroy substances by means of an enzyme-like body which they secrete. The wandering cells posssess, therefore, a double function: the one of dissolving foreign bodies, that they may be washed away by the blood and lymph; the other of first disintegrating these bodies and then carrying them away.

These cells appear in certain morbid processes, being attracted to the proper place, in all likelihood, by chemotrophic influences. Their rôle in disease is merely a broadening and a continuation of their physiological activity. Nevertheless, in our opinion, these cells cannot be regarded merely as scavengers. Even though the end-products of metabolism are

absorbed only in solution, there is nothing to indicate that these cells do not play a part in the transportation of intermediate solid metabolic products. Or, in the vernacular, it might be said that they not only clean the streets, but also take part in the business activities of those who dwell in the street.

These functions of the wandering cells were early adduced in the explanation of immunity phenomena. The theory of phagocytosis, linked with the name of Metchnikoff, has been defended by him with great acumen and against many dissenters.[74] It is beyond question that these cells seize upon micro-organisms, even living ones, for Metchnikoff was able to grow anthrax bacilli engulfed by phagocytes; and it is no whit less certain that the greater number of invading bacteria in certain experimental infections are removed from the inflammatory focus by the phagocytes.

The polynuclear leucocytes constitute an important factor in the fight against bacteria. To them Metchnikoff has given the name microphages, in distinction to the macrophages, the large mononuclear phagocytes which are able to devour and digest foreign cells. The microphages digest the bacteria by means of an enzyme (microcytase) which is analogous to Buchner's alexin; the macrophages, for their part, digest blood-corpuscles and other cells by means of their macrocytase. Metchnikoff leaves open the question as to whether there are only these two cytases, in contradistinction to Ehrlich who conceives of the multiplicity of complement in every species of animal.

The bacteria-destroying cytase escapes from the phagocytes only when they are injured by noxious substances in the blood or in the products of inflammation (phagolysis). In this respect, the views of Metchnikoff and Buchner are diametrically opposed, for the alexins of the latter are assumed to be circulating free in the body fluids. The work of Gruber and Futaki[75] indicates that the outspoken phagocytic power of the leucocytes of the hen toward anthrax is the source of the inherited immunity of the hen to this disease. The same observers found that anthrax bacilli protected themselves against the phagocytes by the formation of capsules, which have no chemotactic influence; but after subcutaneous injection of the same micro-organism into the hen and dog, the bacilli produced no capsules and were immediately destroyed. In the sensitive guinea-pig and rabbit, however, the phagocytes are not of great defensive worth; this is due probably

to complicated biochemical differences between the lymph of susceptible and non-susceptible animals.

As to amboceptor, Metchnikoff's point of view is as follows: In the course of the intracellular digestion of bacteria by the microphages, two enzymes are successively active, the so-called fixateurs, which prepare the ground, and thereupon the microcytase. The fixateurs, in most infections, differ from the cytases in their looser combination with the phagocytes, and in their tendency to an enormous increase in the immuninizing process. Immune sera, therefore, are rich in fixateurs. In the living organism the digestion takes place for the most part within the phagocytes. In the Pfeiffer phenomenon, according to Metchnikoff, there occurs first of all phagolysis in consequence of the injection of injury-producing bacteria, and following this the escape of cytase. Phagocytosis plays a determining rôle in other phases of the Pfeiffer reaction. For example, if an animal immunized to cholera be killed at a time when the inflammatory exudate shows only spores, a careful examination of the peritoneal folds and of the omentum yields many leucocytes filled with vibrios.

That an augmented phagocytosis is the only constant phenomenon observed in the process of immunity is undeniable. We have already called attention to the fact that the factors concerned in bacteriolysis are insufficient to explain all of the elements of an acquired immunity. Indeed, the effect of certain immune sera—Aronson's streptococcus serum, pneumococcus serum, etc.—which are not bactericidal, Metchnikoff ascribes entirely to phagocytic activity. And this view has been confirmed by experiments *in vitro*.

The action of an immune serum, according to this conception, is exerted solely upon the bacteria, even in high dilution specifically preparing them for inclusion in the phagocytes (bacteriotropic serum); and bacteriotropins have been demonstrated even in the bacteriolytic sera of typhoid and cholera (Neufeld).[76] Wright and his collaborators,[77] prior to Neufeld's publication, described the opsonins, bodies found in normal serum, and similar in behavior to bacteriotropins.

Wright has elaborated a most detailed procedure to estimate this action of the serum quantitatively. The patient's serum, and, as a control, that of a healthy individual, are brought into contact

with leucocytes and bacteria and kept at a temperature of 37° C. for fifteen minutes, after which by counting the organisms contained within one hundred leucocytes, the average per white cell can be determined (phagocytic count). The opsonic index is obtained by dividing the phagocytic count of the patient's serum by that of the normal serum. The ratio between two healthy sera is fairly constant, varying only between 0.8 and 1.2; in disease, on the contrary, the index is diminished or very inconstant. Wright has recommended a therapeutic application of the opsonic theory by means of the subcutaneous injection of killed micro-organisms or of their metabolic products (vaccines, see p. 178), this procedure tending to raise the opsonic index. Wright's method is merely active immunization during the course of the morbid process.

Following an injection the index first falls (negative phase; period of antitoxin formation). The dosage must be so gauged as not to produce too great a reduction of the index; and the injection must be so timed as to allow the preceding negative phase to have run its course. The possible dangers attending this last, however, have surely been exaggerated,[78] and Wright himself now insists only that the dosage be such that the general reaction be slight. (Indeed the routine determination of the opsonic index in vaccine therapy has generally been discarded as being too laborious and not necessary. The focal and constitutional manifestations seem to be safe guides for the determination of the dose and the time-interval.—Ed.)

Opsonins and tropins are not identical. The former are inactivated at 56° C., the latter not. Opsonins, further, are supposed to have a complex structure, *i.e.*, composed of amboceptor and complement. Nor can opsonins be grouped with the lysins in the present status of our knowledge. In the process of immunization, tropins, as such, and the amboceptor portion of the opsonins, are increased. The phagocytes are able to destroy certain types of bacterial life, but as this is not true with respect to all micro-organisms, the action of the tropins and opsonins cannot be compared throughout. If we assume that the fixateurs of Metchnikoff are the equivalents of the bacteriotropins, *i.e.*, that their rôle is that of *fixateurs phagocytaires*, then the phagocytic theory and the humoral theory can readily be harmonized. The aggressins, as inhibitors of phagocytosis, fit well into this conception, and are

perhaps to be regarded as the antagonists of opsonins and tropins. The theory of Metchnikoff would accordingly assume a kind of antitoxic immunity, both because the aggressins are credited with a toxic action, and because soluble metabolic products—and there is no essential difference between soluble toxins and the substances of the bacterial bodies—have an aggressin-like power. Indeed, a specific antiaggressin serum has been produced for filtrates of typhoid bacilli. Nevertheless the school of Metchnikoff is firmly of the opinion that the phagocytes *per se* can seize upon even highly virulent bacteria (spontaneous phagocytosis).

Bacillus Carriers.—Even after complete recovery from an infectious disease, an individual may harbor the specific microorganism (bacillus carriers). After cholera and typhoid fever, the causative organism may be isolated from the fæces, and after diphtheria from the mucous membrane of the throat. This persistence of the bacteria may be brief, or a matter of months, years and even decades. Bacillus-carriers can undoubtedly be the source of infection in others, even though the organism may be of an attenuated type, for the latter can readily infect individuals with a lowered resistance. Many endemics are unquestionably due to bacillus-carriers. In protozoon affairs, carriers play an even more important rôle, for here the parasite may persist not only after the conclusion of the disease proper, but even after prophylactic inoculation.

Chemotherapy. Salvarsan.—In the conflict between the living organism and bacteria, the former may be victorious, the latter may gain the upper hand, or there occurs a mutual adaptation in the matter of metabolic products, protective forces, etc. Tolerance represents the stage of perfect adaptation. The host is then a bacillus-carrier. It may happen, however, during an infection that the major portion of the bacteria is rendered harmless, while the more resistant minority survives. These multiply, becoming more resistant to the individual's protective forces, and finally, after a short interval of apparent good health, lead to a recurrence of symptoms. This is probably the case in relapsing fever. The splendid studies of Ehrlich,[79] indeed, have shown that microorganisms can be made resistant to certain well-characterized poisons, as, for example, trypanosomes to atoxyl, to fuchsin and to trypan red, preparations injurious to these parasites, and thus producing atoxyl-fast strains, etc. This resistance to poisons is

inheritable and specific with respect to all the members of a chemical group. This is practically important in showing the necessity of changing remedial agents from time to time, and of combining them; which is in keeping with the most recent work of the Ehrlich Institute showing that trypanosomes may be made to lose acquired characteristics in the process of fecundation and transmission through insects.

These observations have enabled Ehrlich[80] to identify atoxyl, which is so important in the destruction of trypanosomes, as the sodium salt of p–aminophenylarsanilic acid—a discovery which paved the way for the synthetic elaboration of the arsenic domain. By acetylization, for example, sodium acetyl arsinalate (arsacetin) was produced, a body less toxic, but not less potent than atoxyl, and therapeutically, therefore, because of the larger dose permissible, much more efficacious. The foregoing applies, however, only to animals, for in man arsacetin was found to be just as toxic as atoxyl. Some of the trypanosome-destroying substances, the arsenious acids, for instance, act promptly upon the parasite, *in vitro,* while atoxyl and arsacetin, even in a one or two per cent. solution, have no such effect, despite their brilliant action *in vivo.*

Ehrlich has shown this paradoxical behavior to be associated with reduction processes; that is, with the reduction products of atoxyl and arsacetin—these products in turn having a marked reducing power—he succeeded in producing, *in vitro* also, an enormous trypanosomicidal action; while in the animal body, they exhibited an even greater toxicity to the parasites. In the reduction products, arsenic has only a triple valence, similar to arsenious acid, itself intensely potent, but far too toxic for animals.

The problem, then, was to *elaborate* reduction products, not to leave their formation to the animal organism, and to combine these products with other reducing substances. Ehrlich conceived of the cells as possessing different molecular groups, or chemoreceptors, which are able to unite with different combinations, as, for example, trypanosomes with an arseno-receptor and also with an acetico-receptor. If the latter unites more readily with the acetic acid group of the arsacetin than do the cells of the infected animal with the arsenic group, arsenic will be drawn to the parasite and thus the acetic acid group, *per se* harmless, makes possible the arsenic action. In the Ehrlich nomenclature the acetic acid group is parasitotropic, the arsenic itself being organotropic; the

latter, however, plays no part in the process because the parasitotropic groups cause too rapid a union with the parasite. The crux of the matter then was to find molecules or groups which should bind the arsenic element of the poison to the parasite.

On the basis of work carried out along these lines, Ehrlich gave to the world his spirochæticidal preparation 606 (salvarsan), dioxydiaminoarsenobenzol, after convincing himself that the spirilla possessed an amino-oxy-receptor; and he thus paved the way for successful chemotherapy.

Autoinfection.—In individuals who are not demonstrably sick, particularly in those from the milieu of a patient, specific organisms, Klebs-Loeffler bacilli, pneumococci, typhoid bacilli, may often be found. It remains to be determined whether the pus-cocci present on the body surfaces are to be looked upon as relics of an earlier infection, or as pathogenic organisms residing in the ostensibly healthy. These various bacteria are generally harmless, perhaps because the host has been rendered immune by a mild infection. To another, however, they may be virulent; indeed, even in the host himself, they may cause disease if his resisting powers have been lowered (autoinfection).

Conclusions.—We may sum up the question of specific immunity thus: The blood, both under certain normal conditions and after recovery from disease, natural or artificial, is able at times to destroy micro-organisms, to prepare them for phagocytosis and to neutralize their toxic products. In the second place, the phagocytes are capable of engulfing bacteria and rendering them harmless. Both mechanisms, depending upon circumstances, provide the animal body with a defense against harmful bacteria. But neither each by itself nor even the two combined are sufficient in all cases to explain immunity in its entirety. A fuller understanding of these problems will come only with further study.

In what way do certain individuals successfully resist an infection, and why do others succumb? And why do fewer bacteria cause an infection in animals living under ordinary conditions than experimental results would teach? Once again we must fall back upon the protective forces residing in the body-surfaces to explain these individual variations. Even different groups of the same species react differently to microbic invasion. Race, age,

mental depression and a subnormal state of nutrition—all of these are additional factors.[81]

The mechanism of recovery from an infection has an intimate bearing upon the question of the protective forces. In those diseases which exert a toxic action—and in the final analysis, all diseases will probably belong in this category—the result is death if the toxin, because of its amount or strength, can no longer be neutralized. Recovery may occur by the formation or artificial introduction of antitoxin, though cure is sometimes spontaneous. This may occur in tetanus with no antitoxin in the blood,[82] in which case the cells evidently become insensitive to the toxin (histogenic immunity).

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CHAPTER IV

RESPIRATION

The cells of the body continually receive oxygen from the blood and continually give up the carbon dioxide formed in their metabolism to the blood- and lymph-streams. In the lungs the blood takes up a new supply of oxygen and unburdens itself of the carbondioxide it has transported from the tissues. These processes, as a whole, constitute respiration.[1] The interchange of gases between the tissues and the blood is called internal respiration, and that between the blood and the air, external respiration. It is obvious that each is intimately dependent upon the other—the ventilation of the lungs, for example, serving merely to guarantee a fresh supply of oxygen to the blood and the elimination of accumulated carbon dioxide.

External Respiration.—Essential, first of all, to external respiration is an uninterrupted supply of air. A pregnant source of danger is the juxta-position of the air- and food-passages in the pharynx, for foreign bodies that may enter the former often cause grave inflammatory conditions. The mechanism designed to prevent this will be discussed elsewhere (see p. 198).

Means for Removing Harmful Material from the Air-Passages.—The respiratory apparatus is able, as a rule, to rid itself of foreign particles that have passed the defenses at the glottis, or have reached the bronchi in other ways. Of first importance in this respect is **the movement of the epithelial cilia,**[2] which by their slight but constant activity impel such particles from the bronchioles into the larynx. Were we more familiar with disturbances of this protoplasmic movement, we might better understand the underlying causes of certain bronchial and pulmonary diseases.

As the activity of the cilia is probably the most important factor in transporting foreign bodies from the lower to the upper respiratory passages, any disturbance of this movement is obviously a more potent source of harm, in contributing to the stagnation of inflammatory products, than is even the suppression of coughing. Furthermore, since the cilia seem to be whipped on by

inflammatory irritation, it is reasonable to assume that they attempt also to expel invading bacteria, as a defensive measure.

The second mechanism that aids in protecting the lungs is **the secretion of mucus upon the surfaces of the air-passages.**[3] Small bodies, such as particles of coal-dust and bacteria, are caught in this mucus and thereby prevented from penetrating the air-cells; they are then carried away by the action of the ciliated epithelium. When the foreign bodies are inspired in great numbers, however, or the secretion of mucus or the movements of the cilia are hampered by inflammation, these defensive barriers fall away.

The lungs are guarded, further, by our **sense of smell,** which warns against noxious admixtures in the air to be breathed. **Sneezing** also plays a part by keeping the nasal passages clear for the entrance of air. Sneezing begins with a deep inspiration. The powerful expiration succeeding this, forcibly carries with it through the mouth and nose the movable foreign bodies which, by their irritation of the nasal mucous membrane, have initiated the reflex.

Coughing serves as an additional guard and eliminating force. The reflex which induces the act, and which is generally carried by the vagus, may be initiated from the larynx below the vocal cords, from the posterior part of the trachea and the region of the bifurcation, from a diseased pleura, from a pathologically enlarged spleen or liver,[4] and according to some observers, from the stomach and uterus.[5]

The act of coughing begins with a deep inspiration. This is followed by a powerful contraction of the expiratory muscles. At first, the air that should be forced out meets the obstruction of a closed larynx; later, the vocal cords yield to the pressure of the air and the latter is propelled through the opening with great violence. As the soft palate closes the passage into the nose, the current of air carries whatever is in the larynx or trachea up into the mouth. Possibly the contents of the larger, and even those of the smaller, bronchi may be removed by coughing, despite an antagonistic force arising at the bifurcation. In our opinion, however, the movements of the cilia play the main part in transporting material from the alveoli up to the bifurcation of the trachea, whence coughing readily carries it into the mouth.

The impulse setting in motion the mechanism of coughing orig-

inates in the medulla, near the respiratory centre, and responds to stimuli carried by the pneumogastric nerve from the regions already enumerated. That coughing may also be of central origin is indicated from observations in nervous individuals: our ability to cough voluntarily is further evidence.

A reflex cough from the regions mentioned occurs when they have been stimulated beyond a certain point, the degree of stimulation necessary varying, however, with conditions. We may say, in general, that the irritability of the nerves is increased by acute inflammations of the mucous membranes, in which case coughing is produced by abnormally slight stimulation. Certain drugs, on the contrary, as well as certain diseases of the brain, diminish the irritability of the nervous mechanism and thus raise the threshold of stimulation. Chronic inflammation of the mucosa may have a similar effect.

In the first class of cases, coughing may be induced by very slight chemical or mechanical impurities in the inspired air; in the second, no coughing results from stimuli that would ordinarily be effective. An absence or weakness of coughing may likewise result from disease of the motor half of the reflex arc, as has been observed in serious lesions of the nervous system, as well as in any condition of enfeebled musculature. Whatever the cause of the diminished ability to cough, the lungs are endangered because undesirable substances, whether exogenous or endogenous, are not expelled. This danger is much enhanced when the movements of the ciliated epithelium are also hampered. Every physician knows and fears the dangers of such conditions, so often met with in the aged and in those greatly weakened by disease.

The stagnating material readily decomposes, but whether this is due to micro-organisms which are held back simultaneously, or to others which have entered from the larger tubes because of the inefficacy of the defensive forces previously described, is not known. The latter seems to me the more probable inasmuch as many observers have found the normal lungs sterile,[6] though it is true that pathogenic organisms may be present in the lungs of healthy animals.[7] The variations in the depth of respiration and in the number of organisms inspired probably explain the divergent observations. That the bacteria of the inspired air, though relatively few in number, do not always reach the finer

bronchi and the alveoli is due, no doubt, to the various protective forces mentioned above.

The act of coughing is beneficial when it protects the lungs against disease by removing foreign material and excessive secretions, but it is useless when caused by an abnormal irritability of the air-passages, or by reflexes from other organs, because in these cases it has nothing to expel. Here, indeed, it becomes highly undesirable, for it is by no means an indifferent process to the organism. The forcible expirations cause a distinct increase in intrathoracic pressure, thereby interfering with the entrance of blood into the chest, and also a general rise in arterial tension. These may have as their sequelæ the rupture of an artery, an incomplete filling of the heart and a marked pulmonary distention (volumen pulmonum auctum).

Stenosis of the Air-Passages.—External respiration is endangered by any narrowing of the air-passages which hinders the access of fresh air and the egress of vitiated. The significance of such a stenosis depends upon its location. The nasal passages, for example, may be completely blocked, and yet cause only a temporary discomfort and feeling of suffocation, for breathing goes on through the mouth and is not interfered with by eating. To the infant at the breast, however, a severe "snuffles" may render nursing so difficult as to cause grave inanition.

A stenosis situated between the pharnyx and the bifurcation of the trachea has a quite different significance. The obstruction may be the result of pressure from without—struma, mediastinal tumor, aneurism—pressing upon the air-passages, or of disease of the respiratory tract itself, such as an œdema of the larynx. The most frequent site of mischief is at the glottis, for here, especially in the case of children, the passage is narrowest. Illustrative of this are three conditions, characterized by their sudden onset and brief duration. These are pseudocroup, spasm of the glottis and the paroxysm of pertussis. Each, in our opinion, is essentially the result of a spasm of the adductor muscles of the cords.

In pseudocroup, an added factor is an ultra-acute laryngitis, which may be seen under favorable conditions and may persist for hours after the attack has ceased, as is evidenced by the hoarseness and cough. The adductor spasm in this condition is

possibly the result of the inflammatory process; it need not be of high degree to occlude the narrow laryngeal opening of the child.

Whooping-cough,[8] on the contrary, is generally not associated with inflammatory changes. The voice is clear, and the laryngoscopic examination negative. The factors involved in the muscle-spasm—at the basis, apparently, of the paroxysm—are not clear.

Spasm of the glottis (laryngismus stridulus) affects chiefly rhachitic children and is often associated with thymus enlargement and manifestations of tetany. In this connection pædiatricians speak of a spasmophilic constitution.

A stenosis of the respiratory passages would materially curtail the ventilation of the lungs were it not for a compensatory increase in the rate and depth of respiration. This equalizing mechanism is unquestionably the result of a varying activity of the respiratory centre depending upon alterations in the carbon dioxide tension of the blood. A diminished oxygen content, with a correspondingly augmented carbonic acid concentration, is known to render the centre more active. It would be decidedly advantageous, however, if sufficient oxygen were furnished through increased respiratory movements before a change were manifested in the partial pressure of the blood gases.

In the light of more recent studies[9] it would appear that in the stenoses under consideration the respiratory type actually does undergo a change, becoming slower and deeper, and this before the oxygen and carbon dioxide partial pressures in the alveoli are affected. In this way is obviated tissue-injury consequent to oxygen deficiency. In tracheal stenosis, therefore, the alteration in respiration would be of reflex nature and independent of the changes in gas tension.

The effect of a tracheal stenosis is seen in the more forcible contraction of the usual inspiratory muscles and in the innervation from the respiratory centre of new groups of muscles. As the air cannot enter the chest cavity readily, a considerable negative pressure prevails there during inspiration, and the softer parts of the thorax are forced inward by the atmospheric pressure without. The result is the well-known inspiratory retraction of the epigastrium, of the soft tis-

sues above the sternum and clavicles, and of the lateral portions of the chest wall.

The last-mentioned phenomenon, as shown by Gerhardt, can scarcely be due to the direct pull of the diaphragm, for this would demand a downward dislocation of the liver or a marked fixation of the lower ribs. Yet even without these prerequisites, the soft ribs of rickets exhibit a distinct retraction in cases of laryngeal stenosis.

It is to be noted further that the difference between the intra-alveolar and atmospheric pressures in itself creates a not inconsiderable resistance to the inspiratory muscles, and thereby an added respiratory obstruction.

The inspirations accompanying laryngeal or tracheal stenosis are not only more powerful than normal, but more prolonged. This is to be explained on the basis of an automatic regulation (Selbststeuerung[10]) of the duration of the respiratory phases, *i.e.*, when the distention of the lungs has reached a certain point, expiration is initiated by a reflex through the vagus. (The recent experimental studies of Boothby and Berry, however, do not tend to confirm this conception.[11]—Ed.) As the air enters the lungs slowly in tracheal stenosis, a distention sufficient to induce this reflex is delayed and inspiration is accordingly prolonged. Expiration is also lengthened because the air cannot escape readily from the lungs on account of the stenosis, added to which is the inherent inferiority of the expiratory muscles.

Expiration, normally, is a purely passive act due to the elastic recoil of the chest wall and the lungs; but in the conditions under consideration, expiration becomes active through the intervention of certain accessory muscles called into action by the respiratory centre and tending to force up the diaphragm and to compress the thorax laterally. In stenosis of the trachea and larynx, therefore, expiration is lengthened, is more powerful and is converted from a passive into an active process.

During both respiratory phases there may be heard a characteristic stridor as the air passes through the narrowing. The respiratory rate is naturally slower in view of the prolongation of both inspiration and expiration. Another consequence of these conditions is the relatively high position of the lung bases during

the respiratory pause, as is evidenced by observations on the position of the diaphragm in diphtheritic laryngeal stenosis.[12]

This slowing and deepening of respiration is advantageous to the patient; for experimental work has shown that if the trachea be artificially narrowed, such a compensatory mechanism allows more air to enter and to escape from the lungs than is represented by the normal tidal air.[13] Conditions have been shown to be similar in man. Coincident with the increase in respired air per minute is a considerable diminution of the partial pressure of carbon dioxide in the alveoli. It is true that the extra exertion involved consumes more oxygen, but, with the individual at rest, the deeper inspirations enable the supply to meet the demand.

A paralysis of the posterior crico-arytenoid muscles, which separate the cords during inspiration, interferes purely with this phase, for the cords then hang limply and are sucked in by the air as it enters, leaving only a chink between them. This produces an inspiratory stenosis, while expiration is free and unhindered. Membranes and polyps which float loosely above the glottis may similarly give rise to an inspiratory dyspnœa; whereas those below are likely to affect only expiration.

The entrance of air into the alveoli may also be hindered by a narrowing of the coarser or finer bronchi. The results will depend entirely upon the site and extent of the lesion. If the main bronchus on one side be obstructed, the corresponding half of the chest expands less than the other, the normal respiratory murmurs are diminished or absent on this side and a stridor, caused by the stenosis, is heard. The breathing becomes labored, but ordinarily it does not assume the characteristic slow, deep rhythm of tracheal stenosis, evidently because the unaffected side acts as the pace-maker.

Conditions vary with the rapidity of development of a stenosis. If this be sudden, immediate asphyxia may occur, but if gradual, the degree of discomfort may be slight because the individual learns to conserve his oxygen ration by reducing his exertions to a minimum. In this way, individuals with distinctly reduced respiratory capabilities may lead a fairly comfortable existence—how comfortable depending upon the extent of the lesion and upon the oxygen need.

The large bronchi may be narrowed by many of the causes leading to tracheal stenosis, as, for instance, by tumors

or cicatrices from within, or by tumors or aneurisms pressing upon them from without. On account of the large calibre of these tubes, a swelling of the mucous membrane does not ordinarily obstruct the passage of air. In the case of the smaller bronchi, on the contrary, the most frequent cause of obstruction is just such an inflammation of the lining mucous membrane. If only the larger bronchi are involved in a bronchitis, little effect, therefore, is produced upon the interchange of gases in the lungs; whereas if the smaller tubes are affected, the results are far more serious. This is especially true of children on account of the narrowness of their air-passages, and is also true of those with kyphoscoliosis, for their pulmonary surface is thereby already reduced.

In every severe bronchitis, the breathing is superficial and hurried, the rate not infrequently rising to sixty or eighty per minute. Febrile types exhibit the most rapid rate, for fever *per se* accelerates the breathing. The same respiratory changes occur also in extensive non-febrile cases. The factors causing this alteration in the breathing are not understood. A mere retention of carbon dioxide in the blood—the normal respiratory stimulus [14]—will not produce this effect. The conception of a peculiar stimulation exerted by carbon dioxide from diseased lungs is not satisfactory because it is not known that the gas actually does act upon the vagus endings; nor would the carbon dioxide tension in the alveoli be favorable for such a stimulation. It is possible that the inflammation as such stimulates the vagus terminations. In conditions such as pneumonia in which an augmented respiratory volume is out of the question, compensation can be effected only by an increase in rate.[15] Finally, we must not lose sight of the fact that the respiratory changes may be due to the products of incomplete oxidation, comparable to the alterations in breathing accompanying muscular activity.[16]

Bronchial Asthma.—The condition known as bronchial asthma [17] may properly be considered here, because its characteristic paroxysms are assumed to be due to a narrowing of the entire bronchial tree. These attacks exhibit an extraordinarily severe dyspnœa which is independent of the condition of the heart. Usually nocturnal at first, they may later occur at any time and last for hours or days. Though both respiratory phases are powerful and prolonged, expiration is the more

labored. Cyanosis and inspiratory retraction of the soft parts are rarely absent. The breathing is generally hurried. During the paroxysm the lungs are markedly distended, and soon attain the maximum inspiratory position. Auscultation yields profuse rhonchi of all types. Early in the disease patients are comfortable in the intervals, but as time goes on, bronchial catarrh, cough and intermittent dyspnœa are often present.

These asthmatic paroxysms occur particularly as phases of a chronic exudative bronchiolitis (Curschmann).[18] The tough mucinous sputum, Curschmann spirals and Charcot-Leyden crystals speak for a specific process, which Müller,[19] on the basis of chemical sputum analyses, is inclined to regard rather as a disorder of secretion than as an inflammation in the strict sense.

The eosinophilia in the blood and sputum of asthmatics, and also in the membranous discharges of mucous colitis, and further, the neuropathic constitution common to both, have inclined Strümpell to the view that both are of similar origin, possibly an eosinophilic diathesis. Be this as it may, asthmatic paroxysms are practically pathognomonic of bronchiolitis exudativa. Similar paroxysms, it is true, do occur in emphysema; and it may be difficult to determine whether the emphysema or the asthma is primary.

Diverse factors can apparently precipitate an attack, for example, affections of the nasal mucosa, possibly by reflex action. It is conceivable that the mucous membranes of the bronchi and of the nose are affected by similar influences, or that simultaneous changes in both are manifestations of the same (eosinophilic) process.

The most unusual moments may bring on a paroxysm, as, for instance, a peculiar odor, in the asthma of hay fever. One thinks involuntarily of anaphylaxis. The tendency of many observers to regard asthma as the equivalent of anaphylactic sensitization, and to identify the paroxysm with anaphylactic shock, rests upon a certain basis of fact.[20] An unstable nervous organization is common to both. In asthma, furthermore, aerogenic introduction of the provocative material can occur only in minimal amounts, which fits in well with conditions peculiar to sensitization and reinjection in anaphylaxis.

The dyspnœa and the pulmonary distention seen in asthma must first be explained before we can understand the nature of

the paroxysm itself. We have seen that during inspiration—and even more during expiration—there is evidence of a marked obstruction, which is of rapid onset and of relatively short duration, and which quickly leads to a pulmonary distention. What constitutes this hindrance to the passage of air has been variously explained. In the bronchiolitic type it is natural to assume an inflammatory plugging of the finer tubes. More plausible perhaps is an acute non-inflammatory hyperæmia of the medium-sized tubes, in view of the analogous condition of the nasal mucosa; for this would not only permit of a common explanation of these two conditions which seem to be so intimately related, but would also, regarded as a vasomotor phenomenon, be in keeping with the nervous element in asthma. Strümpell[21] happily compares the asthmatic attack with an urticarial eruption, which is also of short duration and a secretory neurosis.

The most acceptable explanation—one accounting for all of the phenomena of the paroxysm—is that of a spasm of the smooth muscle of the fine and medium-sized bronchi superimposed upon inflammatory or vasomotor swelling of the mucous membranes. Experimental studies seem to indicate that pulmonary distention may unquestionably be due to such a spasm. The predominating expiratory dyspnœa would then be ascribed to the narrowing of the bronchioles, with their yielding walls, by the pressure exerted laterally upon the chest wall during expiration; though no other explanation is needed than is given by the loss of elasticity consequent to the pulmonary distention, and by the fact that the expiratory forces are naturally weak.

Vasomotor swelling and bronchial spasm, therefore, explain all of the phenomena of asthma. A spasm of the diaphragm is inconceivable, for the diaphragm, unlike the involuntary muscle in the bronchial wall, can hardly remain in a state of tonic contraction for hours at a time without tiring and, as radiographic studies have shown, does not occur. The symptoms of the paroxysm also fit in well with the conception of anaphylactic shock, both in the vasomotor manifestations and in the intimate association of nervous and muscular factors.

Paralysis of the Respiratory Muscles.—The aeration of the lungs suffers if the thorax or the lungs cannot sufficiently expand and contract. A rigidity of the chest wall alone ordinarily does

little harm, for the compensatory increase in the movements of the thorax as a whole, and of the diaphragm, could move the lungs sufficiently to keep them ventilated.

More serious is disease of the respiratory muscles or of the nerves which supply them. The former occurs in the muscular atrophies and in trichinosis; the latter in peripheral neuritis, or in intracranial conditions such as inflammation, tumor or hemorrhage. The diaphragm and the other muscles of respiration may be paralyzed together or separately. The movements of the diaphragm may be seriously hampered by inflammation of its pleural or peritoneal surfaces, and by abdominal distention whether from fluid, gas or tumor—all of which interfere with respiration by forcing the diaphragm up and by offering an abnormal resistance to its inspiratory descent.

The degree of disturbance of respiratory function from these various causes is closely dependent upon the extent and the location of the disease. Death quickly follows the simultaneous involvement of all of the inspiratory muscles. Of the more limited conditions, equally fatal is bilateral paralysis of the diaphragm, as occurs in disease of both phrenic nerves. A less serious paralysis may not cause death, but merely interferes with the interchange of gases in the lungs. If the compensatory increase in the movements of the unaffected muscles is not sufficient, the vicarious inspiratory muscles, previously referred to, are called upon, leading to bizarre types of breathing, such as the pure costal in a man, etc. The rate may also be increased in these conditions, particularly when pain is a factor.

Loss of Pulmonary Elasticity. Emphysema.—As has already been mentioned, the elasticity of the lungs plays an important rôle in normal respiration, for it is one of the main factors in forcing the air out during expiration. If the lungs are immoderately distended, or if their elasticity is otherwise diminished, the tendency to collapse is more or less lost. Such a loss of elasticity of the lungs, as a whole or in part, may follow diseases associated with violent inspiration or coughing, or those in which the egress of air is obstructed. If a major portion of the lungs has lost its elasticity from overdistention, respiration is handicapped because the distended lung does not exhibit the normal tendency to collapse on expiration, and not being fully collapsed, cannot expand so well on inspiration. Volumen pulmonum auctum,

therefore, diminishes the functional capacity of the lung tissues by rendering it less elastic. Removal of the cause, however, may bring about a restoration of function if the damage is not too great.

Genuine emphysema of the lungs acts similarly by diminishing the pulmonary elasticity. It is more serious than mere overdistention, because the damage it causes is irreparable, and especially because it leads also to an actual loss of lung substance. Many alveolar septa disappear, and the respiratory surface of the lungs is markedly contracted. The loss of the septa leads to an obliteration of many pulmonary capillaries, in this way increasing the resistance to the flow of blood through the lungs. The consequence is an hypertrophy of the right ventricle, evidenced by the accentuation of the pulmonary second sound. Emphysema does not, as a rule, involve both lungs uniformly, but is most pronounced along the free margins in front.

Prominent among the theories advanced to explain pulmonary emphysema[22] are the mechanical and the toxic-inflammatory. According to the former, the elastic tissue suffers purely from mechanical interference with the respiratory movements; while, in the latter, the damage is the result of inflammation and its products. Tendeloo favors mechanical factors because emphysema is most marked where the forces leading to overdistention are most active, and he attributes variations in the resistance of elastic tissue both to congenital inferiority and to acquired injury.

Speaking also for mechanical influences is the fact that although true emphysema is comparatively rare, emphysematous changes secondary to long-continued asthma may be regarded almost as the rule.

Calcification of the first costal cartilage with a resultant rigid distention of the thoracic cage has also been suggested as the chief factor in emphysema.[23] Upon this view is based a surgical treatment of the condition.[24]

Experimental studies have explained the cause of dyspnœa in emphysema on the ground of an unequal arterialization of the blood. As many of the alveoli are rendered functionally incapable in emphysema, oxygenation in the lungs is patchy, so to speak, the result being a disturbance of the oxygen tension in the blood as a whole.[25]

Respiratory Changes of Nervous Origin. Cheyne-Stokes Breathing.—Disturbances of the respiratory centre may also affect the ventilation of the lungs. With an increase in intracranial pressure, the respirations usually become slower and deeper, and frequently, also, more irregular. Anatomical lesions that injure, without destroying, the respiratory centre may give rise to similar effects.

The peculiar type of breathing known as Cheyne-Stokes respiration may be considered in this place.[26] In this condition the respiratory rhythm is broken by pauses of apnœa. After one of these pauses the respirations are at first weak and superficial, but gradually they become stronger and stronger, until they are exceedingly labored. Following the extreme dyspnœa, the respirations gradually diminish in strength until they cease altogether in the period of apnœa, and the cycle of events is completed. Accompanying this anomaly there are frequently manifestations suggesting involvement of other parts of the brain. The patient may lie in a stupor during the apnœa, to awake during the period of dyspnœa with oppressive sensations of air-hunger. The pupils may be contracted and rigid during the pause and become dilated and mobile during the dyspnœa. The pulse is generally unaffected though it may exhibit distinct variations in frequency and tension. Important among the causes of Cheyne-Stokes breathing are uræmia and diseases of the heart and brain.

The explanation of this phenomenon was believed by Traube to reside in an altered irritability of the respiratory centre. Filehne,[27] who observed similar respiratory changes in rabbits under deep morphin narcosis, came to the conclusion, on the basis of comparative respiratory and blood-pressure tracings, that the respiratory centre had become less irritable than the vasomotor. As is well known, blood with a sufficient carbon dioxide tension furnishes the stimulus to both. In the opinion of Filehne, then, the blood is not sufficiently venous during the pause to stimulate the respiratory centre, but does contain enough carbon dioxide to activate the vasomotor centre. The resulting constriction of the arteries going to the brain finally renders the blood sufficiently venous to stimulate the less irritable respiratory centre. The breathing then gradually deepens and the blood becomes better aerated. The vasomotor centre, no longer

stimulated by venous blood, allows the vessels to dilate, and in this way a fresh supply of arterial blood reaches the respiratory centre. The latter is thereby deprived of the necessary carbon dioxide stimulus and the animal stops breathing. Thus the cycle is completed and a new one can begin.

Rosenbach[28] has vigorously disputed this theory. In his opinion, certain portions of the brain, especially the respiratory centre, are rendered less irritable by nutritional disorders, the normal periodic exhaustion being simultaneously increased. He attached no importance, therefore, to variations in the gas content of the blood. Douglas and Haldane[29] have recently shown that by artificially causing an oxygen deficit in the blood, a periodic respiratory rhythm could be produced, and that this periodicity was attributable to changes in the gas tension. How far their results go in explaining Cheyne-Stokes breathing in man, it is difficult to say. Pembrey and Allen[30] showed that the pauses in this phenomenon could be eliminated not only by an inspiratory air rich in carbon dioxide, but also by one with a high oxygen content, and further by a stimulation of sensory nerves.

It is impossible to discuss the various explanations given for this type of breathing, mainly because so few of the facts are known. It should be remembered, however, that even healthy individuals often show a tendency to periodic breathing, as, for example, in sleep; and that many animals normally show this type of breathing. For this reason, the conception that Cheyne-Stokes breathing is due to some disturbance in the nervous connection between the cerebral cortex and the respiratory centre in the medulla, seems especially noteworthy and fruitful.[31]

Changes in the respiratory centre are probably responsible for the abnormal breathing seen in certain intoxications—such, for example, as the spasmodic breathing of hydrocyanic acid poisoing, or the deep respirations of diabetes, uræmia and other conditions—some autointoxications, others acidoses.[32] The latter are characterized by frequent and extraordinarily deep breathing (air-hunger) occurring without demonstrable pulmonary changes. The cause of air-hunger is supposed by some to reside in the increased irritability of the respiratory centre to such acids as carbonic and lactic.[33]

The frequent and superficial respirations of salicylic

acid poisoning, and the various forms of dyspnœa which may be present in hysteria, also seem to be due to nervous influences. And finally, the respiratory centre may be affected by reflexes from various parts of the body, especially from the abdominal organs. The conditions known as asthma dyspepticum, asthma uterinum, etc., are of this nature.[34]

Pleural Effusions. Pneumothorax.—Even though the movements of the chest are normal, and the air can reach the alveoli, respiratory difficulties may arise from a diminution of the total functionating pulmonary surface. Such a diminution may be caused by various diseases, either because they fill the alveoli with inflammatory products, as happens in pneumonia, or because they obliterate them by pressure from without, as happens in large pleural effusions.

When fluid collects in the pleural cavity, the lung at first retracts by virtue of its elasticity; but as the effusion grows, retraction is succeeded by complete collapse. As pointed out by Gerhardt, however, the mechanism is not as clear as was formerly supposed. The tension residing in a pleural exudate is not commensurate with the size of the latter, for in the most massive exudates, Gerhardt[35] found a more pronounced negative pressure than in the intact pleural cavity. That is to say, the lungs may suffer compression, but the mere fact that they are airless is not necessarily the result of such compression. More evidence is needed to explain the factors present here, especially those active in the expansion or collapse of the lung bases.

A pleural effusion does harm in several ways. In the first place, the retraction and compression of the lung on the side of the fluid naturally diminish the surface available for the interchange of gases. Further, since the pressure in the affected cavity is higher than that in the healthy pleural cavity, the mediastinum is dislocated toward the sound side, thus embarrassing the healthy lung as well. The circulation is also materially affected, for the negative pressure normally present in the thorax is diminished, and the venous flow from the periphery toward the heart is consequently retarded. Large exudates may even compress or kink the inferior vena cava. Finally, the increased pressure upon the capillaries of the lungs raises the

resistance in the pulmonary circulation, thus increasing the work of the right ventricle (see p. 19).

If air penetrates the pleural cavity through a wound in the chest wall, or through an opening in a lung produced by such causes as tuberculosis, abscess, gangrene or injury, it gives rise to many of the same results as does an effusion. When such a **pneumothorax** communicates freely with the external air, the pressure in the affected cavity will be the atmospheric pressure. If, however, the perforation closes, a portion of the air is absorbed and the pressure, though less than that of the atmosphere, remains greater than that on the unaffected side. If, finally, the opening be of a valvular nature, permitting air to enter the pleural cavity, but preventing its exit, the pressure within will exceed the atmospheric, at least during rest and expiration, and not only the lung of the affected side, but that of the other also will be subjected to considerable pressure.

The seriousness of a pneumothorax depends mainly upon the functional capacity of the healthy lung. If this can functionate without interference, all the demands of the resting body may be met, even though the pneumothorax should have developed suddenly. Unfortunately, the healthy lung is often encroached upon by the mediastinum, because the latter is thrust past the median line by the high pressure in the affected cavity.[36] When the opening into the pleural cavity is a large one, and admits of free communication with the external air, each inspiration dislocates the mediastinum toward the healthy side and the air cannot enter the sound lung as well as normally. The consequences are less severe if the mediastinum is very rigid or the abnormal opening small. The severe collapse which sometimes follows a large perforation into the pleural cavity may be prevented experimentally by checking the displacement of the mediastinum. In general, a right-sided pneumothorax is more serious than one on the left side, because of the greater capacity of the former.

If the abnormal opening is small enough to prevent any considerable passage of air, the air in the pneumothorax becomes rarefied during inspiration, the lungs expand and pull upon the mediastinum, and the patient may experience practically no discomfort.

These variations in the size of the perforation

and in the degree of mediastinal dislocation explain the extraordinary differences in the clinical picture of pneumothorax, and also why, in surgically produced pneumothorax, the dyspnœa may be relieved by suturing the lung into the opening in the chest wall. The dyspnœa in this condition is clearly the result of the to and fro displacement of the mediastinum and the consequent imperfect ventilation of the still functionating respiratory surfaces.[37]

Modern pulmonary surgery has considerably increased our understanding of pneumothorax. We now know that the all-important factor is the tension in the abnormal pleural cavity. The recent studies on artificial respiration, however, have shown —and this physiologists have long known—that respiratory movements are essential only to a certain degree for the ventilation of the lungs; indeed they are quite unnecessary if an animal be allowed to breathe pure oxygen.[38] This throws considerable light also upon the transportation of air from the medium-sized bronchi to the alveoli in normal respiration.

Bruns found an hypertrophy of the right ventricle in experimental pneumothorax; and his studies, and those of Brauer, indicate that the collapsed lung receives less blood than the other.

If one of the larger bronchi perforates directly into the mediastinum, air rushes not only into the latter, but also into the subcutaneous tissues of the entire body, and a severe cardiac insufficiency may follow.

(It may not be out of place merely to mention the fact that with an increasing knowledge of intrapleural pressure conditions, the field of pulmonary surgery has recently developed apace, confirming the prediction of Billroth, made half a century ago, that "what is now medical will tend to become surgical." The revival of artificial pneumothorax for certain types of pulmonary tuberculosis; the methods of surgical collapse of a diseased lung, particularly those of Wilms and Sauerbruch, and even complete resection of an affected lobe—all of these attest to the foresightedness of the master, at least in the realm of pulmonary disease.—Ed.)

Atelectasis.—An inflammation of the smaller bronchi may decrease the respiratory surface of the lungs, for the œdema of the mucosa easily occludes their lumina, rendering useless the corresponding alveoli. If the occlusion persists for

any length of time, the air in these alveoli is soon absorbed and the condition of atelectasis is established. The oxygen and carbon dioxide are rapidly absorbed, the nitrogen more slowly. The gases are absorbed because the alveoli tend to contract, thereby keeping the partial pressure of the different gases within them at a higher level than the tension of these same gases in the blood.

Atelectasis may also be caused by compression of the lungs, as from large pleural effusions or pneumothorax. Indeed, the alveoli may become atelectatic without bronchial occlusion or compression from without. For example, the portion of the lung which dips into the fluid of a small pleural exudate is not subjected to a positive pressure, and yet it is usually found to be airless. Interference with the movements of the diaphragm, it would seem, may also produce atelectases of this type. The importance of the last, following operation upon the abdominal organs, has probably received too little attention, for to it may be attributed many of the transient so-called pneumonias and hypostatic conditions, which in reality are probably localized atelectases of the lung bases. An added factor in these conditions is the lowering of the general resistance such as follows prolonged anæsthesia, or severe operations even without anæsthesia.

The Effects of an Obliteration of the Air-Spaces.—The disturbances produced by a diminution of the functioning surface of the lungs depend upon several factors, *viz.*, the amount of pulmonary surface thrown out of function, the rapidity with which this occurs, the demands of the body for fresh oxygen and the degree to which an increase in the respiratory movements can compensate for the disabled tissue.

The respiratory movements in conditions of atelectasis are generally deeper and often more rapid, particularly in febrile cases, for the heated blood seems to stimulate the respiratory centre not only directly, but through reflexes from the skin. The breathing may be hurried, however, even in the absence of fever. The explanation of this goes back to the deeper inspirations observed in atelectasis, which are in turn probably due to the stimulation of the respiratory centre by the carbon dioxide retained in the blood. The more prolonged inspiratory movements

enlarge the chest cavity, and, since many of the collapsed alveoli do not expand, the functioning ones must expand all the more. This excessive distention of certain alveoli probably stimulates the vagus endings, thus ending inspiration, as we have seen, and rendering the succeeding expirations prompt and forcible, and thus perhaps increasing the respiratory rate. Accurate analyses of the blood gases or of the alveolar air would furnish a more satisfactory foundation for this theory. Sensory stimuli arising in the lungs may also play a part in accelerating the respiratory rate.

A diminished respiratory surface may sometimes cause a superficial and rapid type of breathing. This is likely to occur in such conditions as dry pleurisy or peritonitis localized about the diaphragm, in which inspiration is curtailed by painful reflexes. The irritability of the respiratory centre is not dissipated thereby, so that a new inspiration follows immediately. Hence the breathing is both shallow and hurried.

In the last analysis, respiratory efficiency depends upon the uniformity with which the air is distributed to the alveoli.[39] In emphysema and in cardiac dyspnœa, the distribution is far less uniform than in health. As the partial pressure of carbon dioxide in the inspired air is low in these conditions, the expired air is also relatively poor in this gas. Hence to bring the carbon dioxide output per unit volume of air up to a normal level, the amount of air taken in and given out in a given time-unit must be increased; and this is synonymous with dyspnœa.

Disturbances in the interchange of gases in the lungs may arise from changes in the chemical or physical character of the alveolar membranes, even though this interchange has been shown to be merely one of diffusion. The dyspnœa of patients with chronic passive hyperæmia consequent to heart disease is probably of this nature.

The Effects of Atmospheric Pressure Upon Respiration.—Variations in the composition of the air must produce certain effects upon the animal organism, for the passage of the gases through the alveolar membranes depends primarily upon the relation existing between the partial pressure of these gases in the blood and in the air-cells. The partial pressure of the oxygen in the lungs may be diminished either by diminishing the atmospheric pressure as a whole, or by reducing the relative proportion

of oxygen in ordinary air. Practically, the latter is seen only when an animal is allowed to breathe in a small air-tight space until the oxygen is reduced. The symptoms produced are those of asphyxia and will be spoken of in that connection (p. 222).

The effects of low atmospheric pressure[40] are frequently seen especially in those who make balloon ascensions, and in those who reach great heights in mountain climbing. The symptoms may be merely unpleasant at first, but at higher elevations they become actually dangerous. The height at which symptoms develop varies for different individuals and under different conditions. Dyspnœa, headache, prostration, paralysis of the extremities, and finally complete unconsciousness may occur during a balloon ascension; and a similar set of symptoms, *viz.*, fatigue, headache, sleepiness, palpitation, nausea, rapid pulse and respiration, and especially dyspnœa, are characteristic of mountain-sickness. In neither case are the symptoms caused by the mere reduction of atmospheric pressure, but are due in part to the cold, the wind, the dazzling light and the bodily and mental strain. That the rarefied air, however, is the main cause of the disturbances, even in mountain climbing, is evident from the fact that symptoms may appear in individuals who do not climb, but are carried up the mountain.

A considerable rarefaction of the respired air may occasion no disturbance in the interchange of gases in the lungs. Most animals and men will endure, without serious consequences, a reduction of the atmospheric pressure from the normal of 760 mm. down to 450 or 400 mm. of mercury; and some can withstand a reduction to half an atmosphere or less. The manner in which the individual breathes is of great importance in determining his ability to withstand these reductions of pressure. Those accustomed to keeping their lungs well ventilated resist a lowering of pressure comparatively well, for they know how to keep the partial pressure of oxygen in the alveoli at a relatively high level. Anything that acts unfavorably upon the mechanics of respiration, such as cold, wind, loss of sleep, etc., renders the individual more susceptible to a diminution in atmospheric pressure. For these reasons there are great individual variations in the ability to withstand rarefied air, and animals, as well as men, living at high altitudes gradually learn to breathe deeply so that the partial pressure of oxygen in their alveoli shall be sufficiently high.

This explains the apparently paradoxical observation that deep breathing, though it adds the factor of muscular exertion, tends to diminish the dyspnœa at high altitudes. A *sudden* change to an atmosphere of low barometric pressure is not so easily borne, hence the symptoms in the first mountain climb or balloon ascension.

According to certain observers,[41] the interchange of gases in the lungs is not affected until the pressure of the external air reaches about half an atmosphere. If the pressure be reduced below this, the elimination of carbon dioxide is markedly increased, and the absorption of oxygen is also somewhat increased, though relatively less so, at least in the early stages.

Observations by Zuntz, however, extending over several weeks, upon persons near the summit of Monte Rosa (elevation 4500 metres) showed in most cases a considerable increase in the consumption of oxygen and in the respiratory rate. More recent studies of the same observer[42] indicate, nevertheless, that this increase, both with the individual at rest and at work, is not so great as was formerly believed. The persons subjected to these experiments did not seem to become acclimated to the changed conditions within the period of several weeks that they spent in the high altitude.

The oxygen-carrying capacity of the hæmoglobin does not diminish at the same rate as does the partial pressure of the oxygen to which it is exposed. Thus Hüfner[43] has shown that with the partial pressure of oxygen at 124 mm.—corresponding to an elevation of 2000 metres—ninety per cent. of the hæmoglobin remains undissociated; at a partial pressure corresponding to an elevation of 4000 metres, eighty-eight per cent.; and at one corresponding to 6000 metres, eighty-five per cent. The decomposition of oxyhæmoglobin may, therefore, be relatively slight at these high altitudes, which accounts for the considerable ability of the animal body to resist reductions of pressure. It is only on the basis of such observations that we can account for the ability of balloonists to ascend to elevations of 10,000 metres and more.

It must be borne in mind, however, that the partial pressure of the oxygen in the lungs may be considerably lower even than is its partial pressure in the outside air. As the blood becomes insufficiently aerated, the respiratory movements are increased and the partial pressure of the oxygen in the alveoli is raised. This

constitutes a most important mechanism whereby the body is able to compensate for reductions in the atmospheric pressure. Muscular exercise sometimes relieves the unpleasant symptoms of a rarefied atmosphere, probably by stimulating the respiratory movements.

In conclusion, we may say that the effects of a high altitude are due mainly to a diminution in the tension of the oxygen, and, to a lesser extent, to other causes. The conditions are very complicated, and it must be acknowledged that various factors, such as circulatory disturbances, may contribute to the production of symptoms. In my opinion, however, the lack of oxygen is the essential cause, a view that is supported especially by the fact that the symptoms of those who ascend to great elevations in balloons are often promptly relieved by inhalations of oxygen.

Increasing the density of the air up to twice the normal pressure is, according to recent observations, without any effect upon the "quality or quantity" of the respiratory interchange of gases. The increased appetite and the emaciation that are seen in individuals subjected to high pressures cannot, therefore, be ascribed to anomalies of respiration.

(An interesting condition is that seen in caisson workers, divers and miners, and which is known as **caisson disease** or compressed-air disease.[44] Here, unlike the conditions enumerated above, the nitrogen of the air seems to play the chief rôle. During compression, this gas is absorbed under great pressure, rapidly saturating the tissues. Saturation takes place quickly, the reverse much more slowly. The danger in this disease resides, therefore, in a too rapid decompression, which leads to the formation of nitrogen bubbles, especially in the venous blood and fatty tissue, and to a dissemination of nitrogen emboli. These emboli lodge chiefly in the spinal cord; hence the prominence of cord symptoms, paraplegia, pains in the legs, etc., in the clinical picture. Pressures of several atmospheres lead to no untoward results if decompression is allowed to take place slowly.—Ed.)

The Inhalation of Poisonous Gases.—The atmospheric air may contain substances which are poisonous to the body. A certain protection against these poisonous admixtures is furnished by our sense of smell, which warns against such gases as ammonia

and sulphuretted hydrogen. In the case of hydrocyanic acid, the odor may be perceived only after the poison has exerted its deadly action.

Carbon monoxide, as usually inhaled, is mixed with gases, *e.g.*, illuminating gas, which possess an odor. Carbon monoxide poisoning is of especial importance because of the marked affinity it possesses for hæmoglobin.[45] When the air contains about one part in a thousand of carbon monoxide, the latter passes into the blood where it unites with a portion of the hæmoglobin in such a manner that the latter can no longer combine with oxygen to form oxyhæmoglobin. If only a small amount of hæmoglobin is thus rendered functionless, the damage is slight, the patient experiencing only a few symptoms, such as headache, etc. If he then breathes good air, the carbon monoxide hæmoglobin is either excreted as such, or the combination is gradually broken up by the mass action of fresh oxygen. In severe cases of poisoning, on the contrary, the blood can no longer furnish the necessary oxygen to the body.

Under such circumstances, the carbon dioxide is excreted through the lungs as usual, but the supply of oxygen is diminished: this becomes dangerous when about one-half of the total hæmoglobin is decomposed. In rabbits killed by monoxide, only twenty to thirty per cent. of the normal amount of oxygen was found in the blood at the time of death. Part of the carbon monoxide in the blood passes into the tissues and there exerts its anæsthetic action. The respiratory centre soon becomes unresponsive, so that respiration ceases entirely: the picture is quite different, therefore, from that of acute asphyxia. If the individual be placed in an atmosphere of ordinary air, or, better still, be allowed to breathe pure oxygen, the carbon monoxide hæmoglobin is gradually dissociated and a recovery may be effected. Considerable light has been thrown upon this subject by improved methods for the determination of the total blood-mass by means of carbon monoxide inhalations.[46]

The Effects of Anæmia upon Respiration.—The supply of oxygen to the tissues may be influenced by a reduction of hæmoglobin. If the quantity of this pigment in the circulating blood be too small, or if it be replaced by some useless combination, such as carbon monoxide- or methæmoglobin, the cells may receive insufficient oxygen. In acute hemorrhage, death results from this

cause when about seventy per cent. of the total hæmoglobin bulk is lost.

If the loss of hæmoglobin or of blood be very gradual, the body can accustom itself to the changed conditions, so that a much greater reduction is possible. We do not know to what limits such a gradual reduction of the hæmoglobin may go, because our clinical methods unfortunately do not determine the total amount of the pigment itself, but only the content of the blood per unit volume. This much may be said, however, that a gradual diminution to one-tenth of its normal bulk can still be endured.

The manner in which the organism accommodates itself to a gradual loss of hæmoglobin is not well understood.[47] It has been suggested that in anæmic states the hæmoglobin undergoes some change whereby it is enabled to transport more oxygen. This view, however, seems scarcely tenable. Furthermore, the total amount of oxygen absorbed and of carbon dioxide eliminated during rest is little, if any, below the normal limits, even though the anæmia be severe. Such patients learn to restrict their movements as much as possible, and so to lessen their need for oxygen; and although the amount of oxygen which they consume during rest is the same as that used by a healthy individual, their gaseous interchange during exercise is much less than normal. Then it is that their lessened ability to transport oxygen is most noticeable; and every physician knows how incapable of exertion anæmic persons are.

Since, in an anæmic person, a small amount of hæmoglobin must supply the tissues with the usual amount of oxygen, at least during rest, it follows that either the hæmoglobin present makes more frequent journeys from the lungs to the tissues, or that it gives up more oxygen to the cells at each journey. Apparently both of these methods of compensation are used. Certain it is that the circulatory rate is increased, for the heart throws out more blood at each beat and the number of beats per minute is increased. Of less importance is the fact that the oxyhæmoglobin is generally more fully utilized. This theory of a more complete utilization of the oxygen supplied to the cells assumes the truth of the current view—and none more satisfactory has as yet been offered—that oxidation up to the end-products of metabolism occurs in the tissues themselves.

The Effect of Circulatory Changes upon Respiration.—If the cells are to receive a proper supply of oxygen, it is not only necessary that there should be sufficient air in the lungs and sufficient hæmoglobin in the blood, but that there be also a sufficiently rapid blood-stream. The hæmoglobin takes up oxygen from the alveolar surfaces very rapidly, and no advantage, therefore, is derived from a slowing of the blood-current through the lungs. When the blood-current is so retarded, however, that the respiratory centre is insufficiently aerated, the cells in the medulla are stimulated and the respiratory movements are deepened. This respiratory compensation is of special value in circulatory disturbances, because it not only maintains the oxygen tension in the alveoli at a higher level, but also directly assists the flow of blood.

Respiratory Compensation.—It is evident, therefore, that conditions which injure external respiration set in motion a compensatory mechanism which is designed to guard against the harmful effects of a lessened internal respiration. The degree to which such compensation is possible depends first upon the magnitude of the disturbance: should an aortic aneurism, for instance, rupture into the lungs, filling the alveoli with blood, no increase, however great, in the depth of respiration can undo the damage. Compensation depends further upon the efficiency of the tools designed for the purpose, *viz.*, a movable chest wall, good respiratory muscles and a strong heart; and these in turn depend upon the age of the individual, his constitution and the soundness of his organs in general. The respiratory needs of the body also influence the extent to which compensation is possible; thus the demand for oxygen when the body is at rest is less than during exercise or digestion. And finally, of importance is the rapidity with which the changes have become established; a gradual development favors good compensation, for persons with disturbances of respiration learn in time to minimize their need of oxygen.

Mention has already been made of the efficiency of this compensatory mechanism in anæmia. Studies have also been made of the gas interchange in other pathological conditions. It has been shown, for example, that in rabbits a pleural effusion or a closed pneumothorax of moderate grade does not influence to any marked degree the quantity of oxygen absorbed or of carbon

dioxide eliminated by the lungs. An open pneumothorax of one side produces equally little disturbance in rabbits and dogs. In man also, the effect of various diseases upon the interchange of gases has been studied by accurate methods. In emphysema, bronchitis, tuberculosis, pneumonia and pleurisy, even when marked dyspnœa was present, the interchange between the lungs and the external air was found to be approximately normal. Yet when there is dyspnœa, additional oxygen is used up by the increased respiratory movements, and, if this were deducted from the total amount of oxygen consumed by such patients, there might prove to be some reduction, after all, in their exchange of gases. The latter seems all the more probable in view of the fact that the respiratory interchange of gases in the above conditions tends to diminish as the hindrance to the entrance of air increases.

It must not be assumed, however, that because the ventilation of the lungs remains practically normal, internal respiration is also unaffected; for it is possible that the tension of the oxygen in the blood might be abnormally low or that of the carbon dioxide abnormally high. Either would influence the interchange of gases between the blood and the tissues. Dyspnœa, indeed, is usually caused by just such changes in the blood going to the medulla.

Asphyxia.—When disturbances of external respiration become considerably greater than can be met by the compensatory mechanism, asphyxia is produced. The symptoms of asphyxia vary with the rapidity of its onset, being milder and less characteristic in gradually progressive cases. Hand in hand with the reduced oxygen content of the blood goes an increased carbon dioxide volume. The latter exerts some anæsthetic effect and when active over a long period of time, as in chronic asphyxia, diminishes the irritability of the respiratory centre to a point incompatible with life. Effects of lack of oxygen, therefore, do not become apparent, because the medulla has been narcotized by the carbon dioxide.

Acute asphyxia is produced by suddenly cutting off the oxygen supply to a brain which is still irritable. Practically, this does not happen very often, but it may result from a filling of the lungs with fluid, from the collapse of a diseased trachea or from a rapidly fatal hemorrhage. The lack of oxygen causes first an increase in the depth and strength of respiration, which is followed by characteristic changes in the circulation. The vasomotor centre is powerfully stimulated, and this causes the

splanchnic vessels to contract, the cutaneous vessels to dilate, and produces a marked rise in the general arterial pressure. As the vagus is also stimulated, the heart is slowed. These changes are designed to furnish the brain with the greatest possible amount of blood, and, thereby, oxygen. In the later stages of acute asphyxia, generalized tonic and clonic convulsions occur, and finally, after a brief period of paralysis, death supervenes.

Internal Respiration.—The internal respiration has necessarily entered at many points into our discussion of the disorders of external respiration, for the two are intimately interdependent. Thus we have emphasized how changes in the internal respiration of the respiratory centre may cause a compensatory increase in the movements of the chest.

The effect of disturbances of external respiration upon the interchange of gases in other tissues remains to be considered. The need of the cells for oxygen is determined primarily by their functional activity; it must be emphasized, however, that the supply must be sufficient if they are to use all the oxygen that they require. It is indeed true that for a time the cells can do without oxygen,[48] because they are still able to fall back upon their intramolecular supply, yet this is of little practical importance.

Normally, the blood carries much more oxygen than is needed by the tissues, and when it leaves them its supply is by no means exhausted. We have evidence that this excess of oxygen is not a useless luxury, but that it is beneficial, and that a relative scarcity of the gas in the tissues is directly harmful. It has been shown, at any rate, that in dyspnœic dogs the proteid decomposition is increased; and although the same has not regularly been proved for man, it suggests the harm which may follow an insufficient aeration of the blood.[49] According to Rosenquist, severe anæmias exhibit periodic increases in the nitrogen output (p. 319), but whether this is due to the anæmia itself, or to the underlying cause of the anæmia, is problematical. It has been shown also that glucose and lactic acid may appear in the urine of dyspnœic animals, and that lactic acid may be present in the urine of dyspnœic men. Finally, the respiratory quotient becomes greater than the normal if the oxygen supply is restricted. Though the explanation of these various findings is uncertain, they tend to show that a dimin-

ished tension of oxygen in the tissues leads to an abnormal metabolism.

In order to estimate the oxygen supply to the tissues, it is necessary to know the amount of this gas in the blood.[50] Unfortunately we possess but little information bearing directly upon this point. In animals with an open pneumothorax, the quantity of oxygen is much diminished in the arterial blood, and it is this diminution that stimulates the medullary centres, causing such powerful respirations that one lung is able to do the work of two. We possess no other data as to the gases in the blood in respiratory diseases. The mere fact that the alveolar interchange of gases does not vary from the normal proves nothing, for this might be true even though the absolute amount of each gas in the blood varied greatly. The cyanosis of many patients with respiratory diseases would lead one to the belief that their blood is rich in reduced hæmoglobin; in some cases this is undoubtedly true, while in others practically normal conditions are found.

Internal respiration may also be primarily disturbed, *i.e.*, by changes in the parenchyma cells or in the tissue fluids. A retarded blood-flow or a lack of functionating hæmoglobin interferes not only with the interchange of gases in the lung, but also with the interchange in the tissues. Primary disorders of the internal respiration may arise when arteriosclerotic changes, thrombosis or embolism interfere with the circulation of a limited area. Compensation is possible here only by the establishment of a collateral circulation. If the cerebral arteries are blocked, the resulting anæmia of the brain produces the symptoms of acute asphyxia. Finally, the displacement of oxyhæmoglobin by carbon monoxide- or methæmoglobin causes a primary disturbance of internal, as well as of external, respiration.

The transportation of carbon dioxide may be affected by changes in the blood, especially those produced by an acid intoxication. The additional acid in acidosis is partly neutralized by an increased formation of ammonia (see p. 327), and partly by some of the fixed alkalies of the blood. This diminishes the free alkali in the blood available for carbon dioxide transportation. In rabbits with severe acidosis, the carbon dioxide content of the blood was found to be reduced from the normal twenty-five per cent. by volume down

to two per cent. Under such conditions, the plasma quickly becomes saturated with carbonic acid gas, and some of the latter accumulates in the tissues. Observers [51] have found, nevertheless, that the blood in severe cases of diabetic acidosis, if under ordinary carbon dioxide tension, can still absorb considerable amounts of the gas—in these cases, at least, invalidating the assumption that there is a disorder of carbon dioxide transportation. Conditions are further complicated by the presence, in human diabetes, of a number of other grave manifestations which dominate the picture. In the acid intoxication of rabbits, the oxidative processes in the body are also considerably diminished, for both the absorption of oxygen from the blood and the elimination of carbon dioxide are reduced. Since the amount of oxygen in the blood is not decreased, the lowered oxidations in the tissues must be referred to changes in the cells, induced perhaps by the toxic action of the retained carbon dioxide. In the acidosis of rabbits, therefore, the retention of carbonic acid gas in the tissues affects both internal and external respiration.

In dogs, and in carnivora in general, much larger amounts of acid are tolerated, for, owing to the relatively high proteid metabolism, much more ammonia is available for the neutralization of any acid present, and for the protection of the fixed alkalies of the blood. Men and carnivora in general, therefore, can resist a considerable amount of acid, disposing of really enormous quantities in some pathological conditions.

Internal respiration finally may be altered by changes in the parenchyma cells, either physiological, as by rest and activity, and by cold and heat, or pathological, as by the various metabolic diseases. In phosphorus and hydrocyanic acid poisoning many of the cells lose, to a variable degree, their ability to take up oxygen and to form carbon dioxide. Though the external respiration and the gases of the blood are both normal, the interchange of gases in the tissues is much reduced, because the cells are poisoned. The animal dies of internal asphyxia; and in prussic acid poisoning the most violent respiratory convulsive movements may result from the asphyxia of the medullary centre.

Respiratory Sensations.—The most important abnormal sensation associated with respiration is that known as dyspnœa. The term has been used by some to designate disturbances in

the respiratory act itself, but we prefer to limit its use to the subjective sensation of an air-hunger. Dyspnœa, in this sense, is always produced by an insufficient gas interchange in the tissues, and especially by a diminution in the supply of oxygen to certain parts of the brain. The associated retention of carbon dioxide is apparently not at fault, for it may be breathed in large quantities without any such effect. Frequently the respiratory movements are increased without any sensation of dyspnœa; in such cases the retention of carbon dioxide would seem to be the important factor in producing the more marked respiratory movements.

How the oxygen is prevented from reaching the brain is immaterial, so far as the dyspnœa is concerned. The respiratory surface of the lungs may be diminished, the blood may flow slowly, or the red corpuscles or the tissue cells may have lost their ability to take up oxygen. Dyspnœa depends rather upon the functional activity of the cells and the degree to which their demand for oxygen is answered; many patients, therefore, experience no discomfort as long as they are quiet. Furthermore, they gradually learn to do their work with a minimum expenditure of energy, thus reducing their need of oxygen, and, in turn, their dyspnœa.

Actual pain may also arise in respiratory diseases. It is generally believed that the lungs themselves contain no sensory fibres, and that what seems to be pulmonary pain is really due to an associated disease of the pleura or chest wall. Severe pain is frequently present in dry pleurisy, and as the latter often accompanies disease of the lungs, it lies close at hand to attribute the pain to the pleural involvement. I am not entirely convinced, however, that this is always the case, for pain may be present in diseases of the lungs unaccompanied by pleurisy.

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CHAPTER V

DIGESTION

The Mouth and Œsophagus.—Digestion includes all of the processes which assist in preparing the food for use in the body. Disturbances of digestion begin, therefore, in the mouth. Here the food is seized by the teeth and is ground up so that it shall present a greater surface to the action of the digestive juices. Serious disturbances may follow improper trituration of the food, whether this results from diseases of the teeth, the maxillary bones or the temporomaxillary joints, or from weakness of the muscles which move the food about within the mouth. If the facial nerves are paralyzed, the food collects in the cheeks and cannot be forced back into the mouth. A paralysis of the tongue interferes not only with chewing, but with the passage of food into the throat. When chewing becomes a painful procedure, malnutrition may be a consequence; for many patients with ulcerations in the mouth, or with inflammations of the tonsils, throat or parotid glands, would rather suffer from hunger than from the pain which is caused by the taking of food. Both the intensity and the duration of such diseases influence the amount of disturbance which they produce.

Stomatitis.—The causes of stomatitis[1] are various. If particles of food are retained in the mouth, they decompose, and the products of decomposition, acting as irritants, may pave the way for the invasion of micro-organisms. Inflammations are especially apt to occur when the growth of bacteria is favored by carious teeth, or when, as the result of severe illnesses, but little saliva is secreted, and the mouth is allowed to become foul owing to the stuporous condition of the patient. The stomatitis which so often accompanies severe diabetes is greatly favored by the caries of the teeth and by the organic acids, both of which are frequently present in the mouths of these patients. The oidium of thrush produces acids, and these undoubtedly irritate the mucous membrane directly and favor secondary infections. Acids and alkalies introduced into the mouth may destroy its coverings and so cause inflammations. The stomatitis of scurvy seems to be of a different character

from that caused by other infectious diseases, for it develops early in the disease, and is particularly severe. The scorbutic gingivitis appears to be a specific effect of the disease, though its true cause is as little understood as is that of the other scorbutic manifestations. (An ulcerative, even gangrenous, stomatitis is a very frequent and diagnostically important manifestation of the acute leukæmias; in this case, the necrosis probably occurs in the areas of hemorrhagic infiltration.—Ed.)

Stomatitis endangers the health of the patient, first of all, by diminishing the ingestion of food—this diminution resulting partly from the tenderness of the mucous membrane, and partly from the loss of appetite caused by the disagreeable taste in the mouth. In the second place, the number of bacteria in the mouth is enormously increased, and vast numbers are swallowed. The ability of the stomach to destroy this material is naturally limited, its disinfecting power often being most reduced in the very diseases with which the stomatitis is associated.

The Saliva.—The different salivary glands produce secretions of variable composition, and each is dependent upon specific stimuli for its activity. We are not familiar, however, with these different factors, and for that reason speak of saliva as the sum of the several secretions. The saliva, in addition to its digestive function, lubricates the food bolus for its passage down the œsophagus, and also, by diluting irritating and corrosive fluids, helps to protect the stomach and œsophagus from injury.

Diminished Secretion of Saliva.—The quantity of saliva is diminished in certain infectious diseases, such as pneumonia and typhoid fever; in certain poisonings, as by atropin; in all diseases which are accompanied by great losses of water, such as cholera, diabetes and interstitial nephritis; and, finally, in those paralyses of the facial nerve that involve the chorda tympani. A diminution of the saliva is always accompanied by a reduction in the activity of the buccal mucous glands. The resulting dryness of the mouth not only interferes with the cleansing of the mouth, but also with the acts of chewing, swallowing and speaking.

To what degree a lack of ptyalin is injurious has not been definitely settled. It was formerly considered that this ferment played an insignificant part in the processes of digestion; but we now know that large quantities of starch are converted into dex-

trin[2] in the mouth and in the stomach by the action of this ferment. The conversion continues in the stomach even after a considerable grade of acidity is present, particularly within the larger particles of food, of which only the surfaces are acted upon by the gastric juice. In addition, saliva can exert a further effect in the intestines where it is reactivated by the pancreatic juice.[3]

Ptyalism.—An increase in the secretion of saliva, so-called ptyalism, may result from an irritation of the chorda tympani nerve as it passes through the middle ear. Impressionable persons frequently have a marked flow of saliva when they think about food, or even when they imagine that they have taken calomel. Ptyalism also accompanies all irritative conditions of the mucous membrane of the mouth, such as may result, for example, from stomatitis. The ptyalism of mercurial poisoning is due in all probability to a central or peripheral stimulation of the nervous connections of the salivary glands. It is possible also that the parenchyma cells are directly affected by the poison. Mercurial stomatitis usually follows the ptyalism and is due to some irritating mercurial compound present in the saliva. This stomatitis will, in turn, increase the salivation, thus establishing a vicious circle.

There is a remarkable increase in the amount of saliva in certain chronic diseases of the medulla oblongata, particularly in bulbar paralysis. This has been compared by some observers to the paralytic secretion which appears in animals after all the salivary nerves have been cut. The latter begins about twenty-four hours after the operation, lasts about one week, and gradually ceases on account of the degeneration of the secreting cells. In both conditions, furthermore, atropin will inhibit the secretion. The two differ, however, in the length of time over which the salivation lasts and in the amount of saliva secreted, the quantity being much greater in the case of bulbar paralysis. It seems to me very probable that the ptyalism of bulbar paralysis is not a paralytic secretion, but is due to an irritation of the cells of the medulla, which occurs as they degenerate. It is comparable, therefore, to the fibrillary muscular twitchings so often seen when the large motor cells of the cord are undergoing degeneration. Certain it is that the saliva is really increased in these cases of bulbar paralysis, and that the condition is not merely a loss of

normal saliva occasioned by a paralysis of the muscles of the mouth; indeed, the salivation is frequently present even before the muscles have become markedly weakened.

An increased flow of saliva may be caused finally by reflexes from other parts of the body, as from an ulcer of the stomach, from the uterus during pregnancy, from the trigeminal nerve in cases of trifacial neuralgia, etc., and by an increased irritability of the nervous system, as in neurasthenia and hysteria.

In all these conditions the saliva presents the characteristics of that obtained by stimulation of the chorda tympani, *i.e.*, it is increased in amount, but poor in solids.

An increased secretion of saliva is especially unpleasant when it drips from the mouth, as happens in cases of bulbar paralysis. Even when it is swallowed it may be disadvantageous, for the large quantity of alkaline, mucous fluid, rich in bacteria, is injurious to gastric digestion.

Composition and Reaction of the Saliva.—The saliva may contain abnormal constituents, such, for example, as the compounds of iodin and bromin, when the latter have been administered. Whether other substances pass into the saliva or not depends largely upon the amount present in the plasma. Urea is thus excreted only in those pathological conditions which increase its concentration in the blood, as in severe nephritis. Other constituents of the blood, such as sugar, rarely pass into the salivary secretion. It is unnecessary to enumerate the various substances which sometimes appear in the saliva, for the subject has but little pathological significance.

The reaction of the saliva varies in the healthy individual during the process of digestion. In the fasting condition it is usually weakly acid, but after taking food it becomes alkaline. On the other hand, in diabetes, in fever and in dyspeptic individuals, it is not infrequently constantly acid, in some instances owing to the presence of the products of bacterial decomposition. The pure parotid saliva is said to be acid in severe diabetes, but the cause of the acidity is not known; and some observers have found it to be alkaline even in severe forms of the disease.

Swallowing.—The passage of food from the mouth into the œsophagus is accompanied by special dangers, for it must cross the respiratory tract in the pharynx. The trachea must be closed off below by the epiglottis, and the nasal passage above by the

soft palate and the superior constrictors of the pharynx. This intricate mechanism is controlled by reflexes through the trigeminal and vagus nerves. The centripetal impulses arise from the mucous membrane of the throat; and the centre which presides over swallowing is situated in the medulla.

Disturbances of the act of swallowing may be caused by a diminished irritability either of the centre or of the sensory nerves. This is seen in certain intoxications, notably in those due to morphin, chloroform and chloral, in diabetic coma and uræmic coma, as well as in some diseases of the nerves. Disturbances of swallowing may also arise from a paralysis of the necessary muscles, caused either by a disease of the motor nuclei in the medulla, as in bulbar paralysis or medullary tumors, or by a neuritis itself, such as is seen so frequently after diphtheria. Furthermore, difficulty in swallowing may arise not from a paralysis, but from a spasm of the necessary muscles, as occurs in hydrophobia, tetanus and hysteria. Finally, defects in the palate, usually caused by syphilitic ulcerations, interfere with the act of swallowing.

In these conditions, the food may pass either into the nose or into the trachea. The latter is the more serious, for if the food with its many bacteria enters the lungs, pneumonia, and not infrequently gangrene, result. The entrance of food into the nasal cavity is less dangerous. Coughing and sneezing are the usual results. Yet these may cause the patient such great discomfort that he refrains from eating; and it is even possible that a large portion of his nourishment may be lost through the nose. When swallowing causes pain, the patient may take insufficient nourishment, just as is the case when chewing is painful.

Œsophageal Stenosis.—Diseases of the œsophagus[4] usually produce symptoms by obstructing the passage of food. This obstruction may be due, in the first place, to a muscular spasm, as in hydrophobia and hysteria (globus hystericus). Such a condition is rarely very serious, because in the case of hysteria it is usually finally overcome, and in hydrophobia there are other more immediate dangers. Occasionally, however, a spasm of the lower end of the œsophagus, particularly at the cardia (cardiospasm), may produce symptoms very like those of a mechanical stenosis. Still, it is not certain that cardiospasm

is not the result of some disorder of the nerve supply, particularly of the vagus.

Of greater importance are permanent obstructions, such as may be caused by the contraction of scar tissue, by tumors or by pressure from without. The milder stenoses interfere only with the swallowing of the coarser foods; the more severe ones may stop even fluids. Normally, we do not feel our food after it has once passed the pharynx; but the patient with an obstruction often complains that he can feel the food stop in a definite place. Above the point of obstruction the œsophagus usually becomes dilated, owing to the stasis of material; and the muscular tissue surrounding the dilatation undergoes hypertrophy. Some of the food which cannot be forced through the narrowed passage stagnates *in situ,* undergoing decomposition. The remainder is immediately returned into the mouth. This regurgitation of food is quite different from vomiting, and the patient himself usually appreciates the difference; for the food swallowed appears to return of itself, the individual experiences no nausea, and his abdominal muscles are not brought into action. Apparently the obstruction to the passage of food increases the contractions of the muscular tissues of the œsophagus. Many believe that the increased pressure on the food simply forces it upward, and that there is no true antiperistalsis in these cases. Personally, however, I see no reason to exclude the possibility that antiperistaltic movements do play a part in the regurgitation of food. (The probability of an antiperistaltic factor is strengthened by the undoubted occurrence, as shown by radiographic methods, of similar waves in pyloric and intestinal obstruction, while in the colon, antiperistalsis is normal.—Ed.)

Pressure Diverticula.—The so-called pressure diverticula[5] usually spring from the upper and posterior part of the œsophagus. They seem to originate from a primary weakness of the œsophageal wall, produced by such causes as foreign bodies, traumatism or possibly congenital defects in the muscle. The wall of the diverticulum is composed of the mucous membrane, the submucosa and a thin layer of muscle. As the sac becomes larger, a part of the food passes into it instead of going down the œsophagus. This food is in part immediately regurgitated, but enough may remain in the diverticulum to press upon the œsophagus and so to occlude it; and it is only after the

sac has been emptied of its contents that a free passage is again opened into the stomach. The symptoms caused by such a diverticulum vary greatly, depending, for the most part, upon the ease with which the sac is filled and emptied. The food which stagnates in the sac may decompose and cause ulcerations of the mucous membrane, and these in turn may give rise to very severe pain. A pressure diverticulum is, therefore, a considerable menace to the health of the patient, and it is fortunate that the condition is a rare one.

Primary Dilatation of the Œsophagus.—Difficulties in swallowing may be caused by a diffuse or localized œsophageal dilatation, unaccompanied by any demonstrable anatomical obstruction.[6] It is very likely that in many of these cases the dilatation is due to a functional stenosis originating in a spasm of the muscle at the lower end of the œsophagus. Such spasms may be primary, or they may be reflexly caused by ulcerations of the mucous membrane. In some instances the dilatation has a congenital origin. The symptoms of such dilatations are very similar to those of ordinary stenoses, *viz.*, obstruction to the passage of food, stasis in the dilated sac and regurgitation. When there is a partial anatomical stenosis, or a functional stenosis from spasm of the cardia, the symptoms may persist for many years with intervals of perfect health. The picture sometimes resembles that of rumination, especially if the dilatation affects that portion of the lower œsophagus which lies between the diaphragm and the cardiac orifice of the stomach.

In another class of cases, the course of the disease is exceedingly rapid, and autopsy discloses an œsophagus widely dilated, filled with food and yet without demonstrable stenosis. A condition similar to this may be produced experimentally by cutting both vagi in the neck of a dog. This operation causes a paralysis of the œsophageal musculature, so that even though the cardia apparently remains open, food does not pass into the stomach, but accumulates in the œsophagus, decomposes and causes death. The cases of acute œsophageal dilatation in man, above referred to, are probably due to a similar primary paralysis of the muscles; and Kraus has described a patient who died of this condition, in whom at autopsy both vagi were found to be diseased.

Painful sensations rarely originate in the œsopha-

gus, first, because painful affections, such as ulcer, are rare in this portion of the digestive tract, and secondly, because this is a comparatively insensitive organ. Yet, as we have already mentioned, diverticula may occasion great pain, as may also spasm of the œsophageal muscles.

Rupture of the œsophagus is very rare. It is usually a complication of some definite lesion of the wall, such as carcinoma or erosion from acids or alkalies. It may, however, occur in apparently healthy individuals, though the cause in such cases is unknown.

The Stomach.—The stomach[7] acts as a reservoir for the large quantities of food which are ingested at each meal. Some of this food is absorbed in the stomach, but most of it, including practically all the water, is gradually passed on into the duodenum, after having been acted upon by the gastric juice. Strangely enough, the opinion has become current that the stomach is a superfluous organ. It is, indeed, true that animals as well as men have continued to live after a practically complete gastrectomy, and that life may be maintained by artificially introducing food into the intestines below the stomach. Indeed, a dog without a stomach may live on quite a varied diet, even though it include decomposing meat. Notwithstanding these facts, it remains true that the less cause a man has to consider his digestion, the better is his health, and the stomach stands as a most important preparatory organ, which receives the varying kinds and quantities of food, and shields the more delicate intestines from the harm which these foods might produce if directly introduced. (An example of the importance of the stomach in this respect is seen in the so-called gastrogenous diarrhœas, occurring in certain cases of gastric achylia and attributed to the entrance of coarse food particles, especially connective tissue, into the intestines, the lining of which is thereby mechanically irritated.—Ed.)

It is possible to obtain pure gastric juice from animals,[8] but from man we are able ordinarily to obtain only mixtures containing both gastric juice and food. In a number of appropriate cases, however, we have been able to study pure gastric juice also in man; these observations have shown the secretion to have an acidity approximately the same as that in the dog, *viz.*, 0.4 to 0.5 per cent. hydrochloric acid[9] (see p. 240).

At the height of digestion, the hydrochloric acid is present

in the stomach in various combinations. In the first place, some has united with the inorganic bases or basic salts of the food, or has even decomposed salts of the weaker acids. Secondly, a portion of the hydrochloric acid combines with certain basic organic compounds. Of these, the most important practically are the combinations between the hydrochloric acid and the various proteids of the gastric contents. These combinations are dissociated by hydrolysis. The generally accepted view is that this loose union of acid and proteid is the essential substratum of what is known as the combined hydrochloric acid.[10] In all probability, however, more complex conditions are influential here.

Finally, a certain amount of free, uncombined hydrochloric acid is usually present in the gastric contents. Yet this may be absent, even at the height of digestion in some individuals, and it is questionable whether such an absence is always pathological or not, for some of these individuals appear to be in a state of perfect health. Organic acids may be introduced in the food, but they are not formed in the healthy stomach; and lactic acid, for example, is never a product of normal gastric digestion.

The total amount of acid secreted depends mainly upon the quantity and quality of the food taken. The secretion apparently continues until the free and combined hydrochloric acid in the gastric contents reaches a certain percentage. Precisely to what degree the secretion of acid depends upon the character of the nourishment, and to what degree it is subject to individual variations, has not been completely worked out.[11]

The Disturbances of Gastric Secretion.—The mucous membrane of the stomach usually continues to manufacture the zymogens of pepsin and rennin, even though the secretion of hydrochloric acid has partly or wholly ceased. Only in the most advanced changes of the mucosa are these ferments much diminished or altogether absent. Such a lack of ferments, constituting the so-called achylia gastrica, may be seen in advanced atrophic gastritis, in carcinoma of the stomach and in certain neuroses.

There is no immediate relation, however, between the secretion of gastric ferments and of hydrochloric acid, for even in the complete absence of the latter, there are considerable variations in the amount of zymogens in the gastric juice. Hence, the

clinical picture of achylia gastrica is by no means well defined;[12] though it may occur in any of the conditions already enumerated, it is often the chief manifestation in individuals who possess simply an irritable digestive tract.

No symptoms are necessarily produced by a mere absence of gastric juice so long as the motility of the stomach remains good, and it is a remarkable fact that this motility is often increased in cases of achylia. We know little of the anatomical changes in the mucous membrane which lead to a cessation of secretion, and we are especially ignorant as to the rôle which nervous influences play in producing this condition. The secretion of rennin (lab ferment) parallels that of pepsin.[13] (And the quantitative determination of the former affords a rough clinical index, likewise, of the amount of pepsin secreted.—Ed.)

What furnishes the normal stimulus to gastric secretion? Pawlow has shown that the most important factor in dogs is the appetite, which is stimulated by sensory influences travelling along the first, second, fifth and ninth cranial nerves. The term "psychic" as applied to this secretion in dogs is an unfortunate one, because it is not strictly such, or at least need not be. Whether the appetite plays an equal rôle in man is still undetermined.[14] At any rate, there is considerable evidence to show that an active gastric juice is secreted when there are certain types of food in the stomach—or more correctly in the pars pylorica—and in the intestines, and further in response to reflexes from other parts of the body. Among substances having this stimulating power are the meat extractives, milk and probably the saliva. Mechanical irritation of the gastric mucous membrane also seems to be a factor.[15]

Just how important in man the appetite is in stimulating the flow of gastric juice must be left in abeyance. It is my opinion that other factors are more significant, *viz.*, ordinary sensory stimuli, the act of chewing and chemical stimulation of the stomach lining.[16] Furthermore, the importance of habit in this regard, as emphasized by Schüle, seems to me vital. In general, I should say that in man purely psychic factors are not of first importance,[17] but rather physical processes with a psychic component. This approaches closely the physiological reflex.

It is possible, too, that some substance secreted by the buccal

mucosa and analogous to secretin, plays a part in the stimulation of the gastric juice.[18] The saliva and the chewing of the food are also seemingly of importance.

Hypersecretion of Gastric Juice.—We are better informed in the matter of variations in the hydrochloric acid content of the gastric juice, though even here, for reasons already mentioned, there are many things that are by no means clear. Most accessible to study are the conditions associated with pathological hypersecretions of the gastric juice.

The stomach of a healthy fasting man is either empty or it contains a small amount of fluid, which may or may not show free acid. Some observers believe that the fasting stomach is always empty,[19] while others hold that it usually contains active gastric juice which sometimes amounts to fifty or one hundred cubic centimetres.[20] In our experience, it has been found empty in some cases, while in others it has contained a small quantity of secretion, possibly caused by material (saliva) swallowed.

(In the past few years, there have appeared many studies devoted to conditions governing the secretion and composition of gastric juice in man. The observations referred to have been made upon individuals with œsophageal stenoses and gastric fistulæ.

Carlson, in a recent report,[21] has given the results of his studies in a young man upon whom a gastrostomy was performed because of a complete cicatricial stenosis of the œsophagus. Confirming, in general, the observations in normal individuals, he found that the fasting stomach contained on an average twenty c.c. of fluid—the range being from eight to fifty c.c. This fluid was made up in part of the secretion of the gastric glands and also of material that had regurgitated from the duodenum. The daily and seasonal variations noted, he has attributed to differences in tonicity of the empty stomach, which allow a varying amount of duodenal contents to flow back.

Furthermore, differing with Pawlow, and, in the main, agreeing with Boldyreff, in their animal studies, Carlson has found that the gastric glands in man are in a state of continuous secretion, the juice being poor in hydrochloric acid—especially when the rate of secretion is slow—and rich in pepsin. This continuous secretion varied from

two to fifty c.c. per hour and seemed to depend upon several possible factors, such as the vagus secretory tonus, and the action of products of the auto-digestion of the gastric juice itself. Carlson, on the basis of his own observations and those of others working under similar conditions, has estimated that a normal adult secretes an average of fifteen hundred c.c. gastric juice in the course of a day.

The seeing, smelling and thinking of food caused only a slight secretion of gastric juice in Carlson's subject; this he has attributed to the fact that he had to do with an individual for whom the taste of food was essential. Pawlow has also observed considerable individual variations in dogs in this respect.

The pure gastric juice obtained from these patients with fistulæ, by different investigators, contained from 0.35 to 0.5 per cent. of hydrochloric acid. This percentage, though considerably higher than that usually given for human gastric juice, has been rather constant in different individuals, and in the same individual under different circumstances; so much so that Bickel believes that what is usually designated as hyperacidity in man is in reality a hypersecretion. The excessive production of gastric juice merely raises the percentage of acid in the mixture of juice and food which is subjected to the ordinary clinical analysis. Even in the most marked instances of "hyperacidity" the total acid in the gastric contents does not exceed that of normal pure gastric juice.

Of other factors which influence gastric secretion may be mentioned anger, which decreases the secretion in both man and dogs. Furthermore, as necessary conditions of secretion, the body must contain sufficient water and sufficient chlorids. A deficiency in either causes less gastric juice to be secreted, without, however, influencing its strength.—Ed.)

Pathologically, the stomach may contain large amounts of fluid, even when the individual is fasting. The percentage of hydrochloric acid in this abnormal secretion may be low, or it may equal that of pure gastric juice (circa 0.5 per cent.). At the height of digestion, such patients also exhibit a variably acid secretion.

Hypersecretion[22] may occur as a continuous, or —and this is the more frequent—as a periodic condition in certain general disturbances of the nervous system, such as

fever, hysteria, migraine and neurasthenia, or as evidence of a local lesion, notably gastric ulcer. Occasionally, the gastric disorder associated with hypersecretion appears, in a sense, to be primary (dyspepsia acida). In some cases, the amount of juice poured out seems to be particularly large when digestion is at its height (digestive hypersecretion).

The cause of the hypersecretion appears to be an increased irritability either of the mucous membrane of the stomach or of its secretory nerves. In many cases, even after a long period of hypersecretion and hyperacidity, no anatomical changes are demonstrable in the gastric mucous membrane,[23] which would seem to indicate that, in these cases at least, the condition is of nervous origin. It is possible that a hypersecretion is sometimes caused by a stimulation of the secretory centres in the brain, and when this is so the condition may be comparable to the salivation that is so often present in progressive bulbar paralysis.

Hyperacidity. Ulcer of the Stomach.—In still other cases,[24] the stomach in the fasting state is normal, but at the height of digestion exhibits a percentage of acid as high as that of pure gastric juice, *i.e.*, 0.4 to 0.5 per cent. This condition of simple hyperacidity probably arises in different ways. It might be looked upon, for example, as the result of the secretion of an abnormally acid gastric juice; while, on the other hand, the conception of an increased secretion of normal acidity, especially if combined with motor insufficiency, would explain conditions no less satisfactorily.

Attention has already been called to the very frequent association of hypersecretion and hyperacidity. In gastric ulcer, however, a pure hyperacidity is not infrequently met with. The relation between the two is of particular interest, because some observers look upon the hyperacid condition as the cause of the ulcer. In animals, tissue defects of the gastric mucosa, produced by trauma or otherwise, nearly always heal rapidly.[25] The wall of the stomach opposite the point of injury contracts, thereby protecting the abrasion, to a certain extent, from the action of the gastric juice and enabling the epithelium rapidly to bridge over the defect. In man, on the contrary, gastric ulcer is characterized by its extraordinary chronicity.

A double etiological relation seems to exist between hyperacidity and round ulcer of the stomach. On the one hand, the irritation of the nerves at the base of the ulcer apparently increases the secretion of gastric juice; while, on the other, a hyperacidity would interfere with the healing of any defect in the mucous membrane, and an anatomical lesion would, therefore, be more apt to lead to a chronic ulceration. Chronicity would also be favored by local vascular disease, in particular by thrombosis of the smaller gastric arteries,[26] by vasomotor irritability and by constitutional disorders, such as anæmia. The greater the hyperacidity, the more readily would abrasions go over into chronic ulcer. The excess of acid acts not by digesting the injured area, but by interfering with the formation of granulations. Healing naturally becomes more difficult if the defect has existed for some time, and induration of the margins and base has occurred. The view that an absence of antipepsin plays a rôle in the etiology of round ulcer still lacks confirmation.

Certain recent observations[27] have emphasized the rôle of infectious processes in the production of gastric ulcer. Mycotic necroses of the gastric mucosa do indeed occur, and it is conceivable that these are transformed into genuine ulcers by the joint action of the bacteria and the gastric juice. (Rosenow, among others, has produced ulcer of the stomach by the injection of streptococci.[28]—Ed.)

The etiology of gastric ulcer is far from clear. Not infrequently, for example, hyperacidity is not present, and on the other hand a high degree of acidity is often unaccompanied by ulcer. (The cause of the original tissue defect is perhaps more readily understood than is the reason for its failure to heal. Chronic ulcers have been produced in rabbits by section of the vagi,[29] though in what way is not known. In dogs, the feeding of colon bacilli[30] has likewise proved successful. The action of the acid gastric juice probably plays an important part, either directly by its corrosive effect upon the ulcer, or indirectly by causing a spasm of the pylorus, delayed emptying and further accumulation of acid material.[31]—Ed.)

Effects of Hypersecretion and Hyperacidity.—In discussing the effects of an excessive secretion of hydrochloric acid, it is possible to consider hyperacidity and hypersecretion together. Disturbances are produced by the excess of acid; and these occur

during digestion in cases of pure hyperacidity, during fasting in cases of hypersecretion, and during both states when the two are combined. As Riegel has said, the results in all cases are due rather to the profuse secretion than to the high acidity of the juice secreted. In the presence of an excess of acid, the digestion of starch in the stomach ceases altogether. The proteids are digested, but whether normally or not is not known. The patient frequently suffers from severe pain and from vomiting, for both of which the hyperacidity is usually directly responsible, for they are generally relieved by the administration of substances which will combine with acids, such as alkalies and proteids.

The effect of an increased secretion upon the gastric motility will be discussed in another place, though we may mention here that not infrequently a hypersecretion is followed by dilatation of the stomach (Riegel). What effect the hyperacid gastric contents exert upon the intestines and upon the intestinal digestion is not definitely known. Possibly the poor nutrition of many patients with hyperacidity is due to the difficulty in neutralizing the hyperacid material which reaches the intestines and to a consequent insufficient absorption of nourishment. But, as a rule, this is not the only cause of their poor nutrition; the pain, the partial starvation caused by the fear that food will cause pain, and the loss of material by vomiting, all tend to produce emaciation. Constipation is also frequently associated with hyperacidity.

The symptoms of gastric ulcer are, in part, those of hyperacidity; yet the pain is usually more intense, probably because the base of the ulcer is especially sensitive. The pain may be very severe, however, even though there be hypochlorhydria. Then, too, a series of complications may follow in the train of the ulcer. Arteries may be eroded and hemorrhage ensue; the gastric wall may be perforated with resultant adhesions, abscesses or peritonitis. The number of such complications is unfortunately a large one.

Subacidity and Anacidity.—A diminution of gastric acidity is met with distinctly more often than is an increase. A certain caution, however, is indicated in the interpretation of diminished acidity, for the causative factors are complex. The amount of free hydrochloric acid may be lowered, or free acid may be en-

tirely absent; in either case the total acidity may be low, or normal or even higher than normal. The absence of free acid does not necessarily mean that none is being secreted; for acid poured out in normal amount may combine with unusual avidity, particularly with proteids. We can form no idea of the total amount of acid secreted, because of the intimate relation in man between the quantity secreted, reabsorbed and propelled into the intestines.

Free hydrochloric acid is absent in many acute gastric disturbances, functional as well as anatomical, notably in those associated with the acute infectious diseases. Anacidity is seen more frequently, however, in chronic diseases of the stomach, as in atrophy or amyloid degeneration of the mucous membrane, and especially in carcinoma. Diseases of other abdominal organs—of the liver, for example—may also inhibit the gastric secretion; and general conditions such as pernicious anæmia, advanced tuberculosis and cachexia may all be associated with an absence of free hydrochloric acid in the gastric contents. A complete anacidity, however, does not develop rapidly, but is the result of a gradual fall from the practically constant and not inconsiderable degree of free acidity seen in health, under fixed external conditions. This gradual approach to total anacidity is common in the chronic dyspepsias.

We have already emphasized that a decrease both in free and combined acid may be the result of diverse factors. As the secretory conditions in a healthy individual who leads an even and regular life are fairly constant[32]—and incidentally different from those under which pure gastric juice is obtained—we must assume that there is some regulating mechanism at work, the action of which is easily and often disturbed in pathological conditions, and not infrequently even in health, when the routine of a regular existence is upset.

The two conditions adduced in explanation of an acid reduction have already been alluded to, *viz.*, an actual diminution in the amount of gastric juice secreted—whether there is a pure secretion containing less acid is not known—and secondly, the production in considerable amount of substances which combine with free acid.[33] The last is, undoubtedly, true in carcinoma of the stomach, for hydrochloric acid continues to be secreted in

this condition; while the amount of combined chlorid may not only equal, but exceed the normal.[34]

Clinical experience speaks also for this second hypothesis. Thus free acid may be present in carcinoma; this is the rule, in fact, in the early stages, particularly when the carcinoma has developed upon the site of an old ulcer.[35] It is more difficult to understand the anacidity associated with malignancy of neighboring communicating structures, as, for example, the œsophagus and gall-bladder.

When the hydrochloric acid in the gastric contents is reduced, the ptyalin is able to act for a long time upon the food, unless its activity is interfered with by the presence of organic acids. Digestion of the proteids is usually diminished or absent, according to the reduction in the amount of hydrochloric acid.[36] (A carcinoma of the stomach, however, apparently produces ferments capable of causing an even deeper cleavage of proteids than does pepsin.[37] The use of one of these ferments, which will split glycyltryptophan, has been suggested by Neubauer and Fischer[38] in the diagnosis of gastric cancer. The test as originally employed, and some of its modifications, seem to have a certain value, when disturbing factors such as the regurgitation of the duodenal contents can be eliminated.—Ed.) A diminished proteid digestion in the stomach does not necessarily mean a loss of food material to the body, for with a proper dietary the intestinal digestion can compensate for the inefficiency of the stomach, and the nitrogenous material in the body may not only be maintained at the old level, but in some cases the store may be actually increased (v. Noorden). And I am convinced that nitrogen equilibrium may be conserved even with individuals on ordinary diet, for many such, despite the anacidity, are quite free from symptoms.

Bacterial Action in the Stomach.—The normal gastric juice possesses decided antiseptic properties, owing principally to its acidity. Whether the pepsin is of great importance or not in this respect is still a matter of dispute. Cells are usually digestible only when they are dead; yet, in the opinion of some, pepsin plays an important part in limiting bacterial growth, more especially the growth of those organisms which give rise to lactic acid fermentation. An acidity of 0.2 per cent. in a test-tube will, after a long time, destroy many bacteria, such, for example, as the

typhoid bacillus, the cholera vibrio and the bacteria of decomposition and fermentation; whereas other organisms, and especially spores, are not greatly injured by this amount of acid. Yet conditions in the test-tube are not the same as those in the stomach. Many parts of the food do not come into intimate contact with the gastric juice at all, either because they are quickly passed on into the intestines, or because they lie in the centres of large particles which are not broken up in the stomach. Furthermore, a large part of the hydrochloric acid secreted is immediately bound by the proteids, etc., and these combinations are known to be less antiseptic than is free hydrochloric acid, though even they may kill cholera bacilli. It is evident, therefore, that the bactericidal powers of the gastric secretion are limited, and that numbers of micro-organisms are constantly being passed on into the intestines.

On the other hand, an abundant multiplication of bacteria within the stomach is prevented mainly by the normal evacuation of its contents. Even though hydrochloric acid is absent, no bacterial decomposition ordinarily takes place so long as the motility of the stomach remains good and its contents are regularly passed on into the intestines before the bacteria have time to multiply. The condition most favorable to bacterial decomposition is the stagnation of material in the stomach; when this last is present, the grade of acidity plays a most important part in the determination of the variety of micro-organisms which shall multiply, and this in turn determines the character of the decompositions that shall take place.

If free and abundant hydrochloric acid be present in stagnated gastric contents, the ordinary putrefactive decompositions of proteid material rarely take place. The fermentation of carbohydrates, however, does occur: sugar is transformed into alcohol and carbon dioxide, alcohol into acetic acid, dextrose into lactic acid, butyric acid, carbon dioxide and hydrogen, etc. The gases which ordinarily result from these fermentations are carbon dioxide, hydrogen and traces of methane. These, together with swallowed air, usually make up the bulk of the gases present in the stomach during gastric fermentations. Each of these fermentations may be carried on by a number of micro-organisms that will resist an acid reaction

of not too high a grade;[39] but yeasts and sarcinæ are those most commonly found. Occasionally, similar fermentative processes occur even though the gastric acidity is very high. Here, possibly, the products of fermentation cause a reflex flow of gastric juice.[40]

If the stagnation is accompanied by a diminution or absence of hydrochloric acid, then opportunity is given for the multiplication of a greater variety of micro-organisms. These may even cause putrefaction of proteid material. More frequently, however, they give rise to fermentative processes similar to those just described. Yet there is a special tendency to the production of lactic, butyric and other volatile organic acids.[41] Lactic acid fermentation is particularly characteristic of gastric stagnation in the absence of hydrochloric acid; and if this be present in sufficiently large quantities it tends to inhibit the growth of many bacteria which would otherwise give rise to putrefactive processes. A special lactic acid bacillus (Oppler-Boas bacillus) is then frequently present in enormous numbers in the gastric contents.

From a consideration of these facts, it will be seen that no one kind of bacterial decomposition is pathognomonic of any particular clinical condition. The decomposition depends rather upon the varieties of micro-organisms which have been introduced into the stomach, upon the opportunity which they have had to multiply and upon the kind of food which is subjected to their activities. The relation between carcinoma of the stomach and lactic acid fermentation must be judged from such a general stand-point. The two frequently occur together, but this depends upon the fact that stagnation, absence of free hydrochloric acid and diminution in the ferments —the very conditions which favor the development of lactic acid fermentation—are most frequently present in cancer of the stomach. If, as rarely happens, the combination of a gastric stagnation and an absence of free hydrochloric acid is caused by some condition other than carcinoma, lactic acid fermentation might occur; though some maintain that lactic acid is formed only in the presence of a ferment-like body, which is found in cancer tissue, blood-serum, etc.[42] Very remarkable decompositions have been observed in some stomachs, for example, the production of sulphuretted hydrogen, when free hydrochloric acid was absent.

The acidity of the gastric contents exerts no small influence upon the chemical processes in the intestines,[43] and we may say here that, in general, as the acidity in the stomach diminishes, the putrefaction in the intestines tends to increase. This subject will be more fully considered below.

It sometimes happens that fermentation occurs in the gastric contents, even though there is no diminution either in the secretion of acid or in the motility of the stomach. In such cases it is possible that the condition is due to the introduction of excessive amounts of fermentable material, together with the agents which cause the fermentation.[44] The latter would in turn affect the gastric motility, and a disturbed motility would favor further fermentation.

Abnormal fermentative processes do harm to the stomach in various ways. The products of fermentation may irritate and injure the gastric mucosa, producing loss of appetite, pain, vomiting and possibly spasmodic closure of the pylorus with diminished gastric motility. Gases may be produced in large quantities, causing abnormal distention and belching. The abnormal secretion of fluid by the stomach, together with the distention by gases, would favor the development of gastric dilatation. At times, toxic substances are produced in gastric fermentations, and these may give rise to a varied category of general symptoms (see p. 255).

We know very little about the function of the mucus secreted by the stomach, which is unfortunate, because it is quite probable that this may exert some protective influence in certain pathological conditions. The amount of mucus secreted in diseased conditions varies greatly; and it is present in different forms,[45] depending upon the action of hydrochloric acid. At times, possibly, there may occur a hypersecretion of mucus on a nervous basis,[46] similar to a hypersecretion of gastric juice.

The Disturbances of Gastric Motility

The normal movements of the different parts of the stomach are fairly well known.[47] The fundus acts as a reservoir for the food. Its wall shows peristaltic movements, but the pressure within it is comparatively low. The antrum pyloricum contracts periodically, several times a minute, although it may at times

contract irregularly. During a contraction, the pressure exerted upon its contents is considerable, being over a half metre of water in man. Since its cavity is shut off from the fundus by the sphincter-like action of its proximal portion, its contents may be propelled into the intestines only when this muscular ring relaxes. (The opening and closing of the pylorus is in part, at least, dependent upon the so-called acid-reflex (Hirsch, Serdjukow, Cannon).[48] Relaxation of the pylorus occurs when free hydrochloric acid appears; and when the acid contents thus released reach the duodenum, they not only initiate a reflex which closes the pylorus behind them, but also stimulate the flow of the alkaline pancreatic secretions. The latter, in turn, gradually neutralize the acid material which has reached the intestines, and thus permit of another pyloric relaxation, and the repetition of the cycle.

Other factors, however, seem to be influential in this mechanism.[49] Thus in dogs, the mechanical irritation of coarse food particles keeps the pylorus in a contracted state; and infiltrations of the gastric wall, even though at a distance from the pyloric end, affect its opening and closure. An illustration of this last is the pylorospasm of gastric ulcer without hyperacidity. On the other hand, a carcinoma not situated at the pylorus may, with normal conditions of acidity, be associated with a permanent pyloric insufficiency. And, finally, pyloric insufficiency, and particularly pylorospasm, may exist in the complete absence of gastric and duodenal changes. This nervous type of spasm may be provoked by morphin, physostygmin and cold, and ended by means of atropin and papaverin.

The pyloric play, so-called, is therefore of a more complex nature probably than has heretofore been supposed. Possibly innervation factors as yet little understood play an important part.—Ed.) The antrum pyloricum seems to pick the fluid and finely divided portion of the gastric contents out of the fundus, and in this manner to regulate still further the emptying of the stomach.

The cause of the gastric movements is very uncertain. In the first place, like all other unstriated muscles, the stomach has periods of rest alternating with periods of activity. Some have believed that the acidity exerts a great influence upon the gastric movements, yet we know that under pathological

conditions at least, no definite relation exists between the motility of the stomach and the acidity of its contents. The delayed emptying seen so often in cases of hyperacidity may be ascribed to an increased activity of the duodenal reflex mentioned above; while the rapid emptying, on the other hand, associated with diminished and absent acidity, is probably due to the weakness of the pyloric reflex, and may be regarded as the rule in achylia gastrica. The consistency of the contents certainly influences gastric motility. Large solid particles are thrust back into the fundus by the antrum, whereas soft masses are allowed to pass through into the intestines. Warm material tends to increase the peristalsis and to relax the pyloric sphincter.[50] Although careful studies have been made as to the length of time that certain foods remain in the stomach,[51] more work is needed upon abundant mixed diets.

(Cannon, in his work on cats, has carefully studied the effects of different foods, singly and combined, upon the activity of the pylorus. Carbohydrates, which make little demand upon the gastric acidity, pass quickly into the duodenum. The proteid curve is a gradual one because this food unites with the first acid secreted, and thus delays the appearance of sufficient free acid to provoke the pyloric reflex. Fats likewise remain for a long period in the stomach because of their known inhibitory effect upon the secretion of acid. Cannon has also elaborated the action of combinations of these foods.—Ed.)

Increased Peristalsis and Increased Gastric Motility.—At times the peristaltic movements of the stomach are increased, and its contents are emptied more rapidly than normal. Yet this rapid emptying does not necessarily occur; for, when a hindrance to the exit of food is present, the powerful contractions of the muscle may be unable to expel the food even within the normal period of time. Frequently the patient is rendered extremely uncomfortable by the excessive gastric peristalsis, and the movements of the stomach may be plainly visible through the abdominal wall. In some cases this condition of "peristaltic unrest" is dependent upon a primary pyloric stenosis; in others, it is probably caused by an excessive irritability of the nervous connections of the stomach, and it is then frequently accompanied by violent peristalsis of the intestines. As we have already said, the stomach may empty itself with unusual rapidity in achylia

gastrica, though in this case there are usually no associated sensations of increased peristalsis. We must be cautious, however, in linking a rapid emptying with any particular secretory anomaly, for hypermotility may occur also with hypersecretion.[52]

Motor Insufficiency and Gastric Dilatation.—Much more frequent than an increased is a diminished gastric motility, and a consequent delayed or incomplete emptying of the organ. This is seen, among other conditions, in acute and chronic gastritis, and particularly in carcinoma. Cancer may act in this way not only when it causes an anatomical pyloric stenosis, but also when it is situated in regions the involvement of which has no relation, necessarily, to the emptying of the stomach. In this case, the disturbance of motility is associated with anomalies of secretion; the interaction of the two, however, is not understood. Either may be the consequence of the anatomical lesion, or the secretory disorder may lead to the motor insufficiency. Yet the latter not infrequently occurs primarily, the secretory conditions being quite normal.

We are as yet unacquainted with those factors, a knowledge of which would be most instructive, *viz.*, what lesions of the nervous apparatus and of the musculature underlie these motor disorders, and to what extent is the muscle of the antrum and of the fundus crippled. Possibly Moritz's method of estimating the pressure in the different parts of the stomach will prove of value in this regard.[53]

The motility of the antrum, and particularly of the pylorus, is obviously intimately influenced by what would seem to be insignificant factors, not only under pathological conditions, but even in health.[54] I am of the opinion, indeed, that gastric pathology is much more a matter of motor than of secretory disturbances. The prominence of the latter in diseases of the stomach is due to the fact that our methods of estimating motor disorders are too little refined. Even rœntgenoscopy is not entirely satisfactory, because it carries with it the use of an abnormal meal which in itself may affect gastric motility.

The effect of a motor insufficiency is that the stomach does not empty itself as quickly as a normal organ under the same conditions. So long as the degree of insufficiency is slight, this is the only consequence. If, on the contrary, there is a considerable stagnation of food, which in decomposing builds

substances such as gases which distend the stomach, or such as fatty acids, which injure the mucosa; and if, further, secretory anomalies exist which favor the decomposition of the stagnant material, then the motor insufficiency leads to dilatation. The secretion of fluids in large amount also predisposes strongly to dilatation in view of the insignificant power of the stomach to absorb them. That food stagnation may produce secretory disturbances is indicated by the studies of Kausch, in which a change in secretion was observed after a successful gastro-enterostomy.[55]

Causes of Dilatation.—Dilatation may result from a variety of causes. In the first place, it may follow a mechanical stenosis of the pylorus, such as may be caused by tumors, contracted scars or pressure from without. It is quite probable also that it may follow a spastic contraction of the pyloric muscle, which arises from reflexes from ulcers, from sensitive spots on the mucosa or perhaps from the irritation of a normal mucous membrane by caustic substances or even by hyperacid secretions. In the latter case, it is the duodenal mucosa and not the gastric, as formerly supposed, that seems to initiate the reflex.[56] In infants, a primary pylorospasm is not infrequently observed.[57]

Every stenosis of the pylorus increases the work of the muscle in the antrum pyloricum. This additional work causes the muscle to hypertrophy just as additional work elsewhere will lead to an hypertrophy of the corresponding muscle. The more powerful contractions of the hypertrophied gastric muscle may for a time neutralize the effects of even a considerable stenosis. To what extent this is possible depends upon the strength of the hypertrophied muscle. Ultimately the hindrance to the exit of food may exceed the compensatory power of the antrum, and the stomach will no longer be able to empty itself completely. Dilatation then begins, and this is frequently favored by a concomitant weakening of the antrum caused by a degeneration of its smooth muscle-fibres.

Anomalies in the form and position of the stomach may also lead to dilatation.[58] Our former ideas as to the position of the organ have undergone complete revision as a result of radiographic methods of examination.[59] As a rule it lies perpendicularly with an upward kinking at the pyloric antrum (siphon form of Groedel). Changes in its im-

mediate surroundings, tight lacing, enteroptosis—all of these exercise a most pronounced influence upon the ability of the stomach to empty itself. Such conditions may cause, in the first place, an actual narrowing of the gastric outlet, as happens, for example, when an abnormally low stomach presses upon or kinks the duodenum. Then, too, the low position of the fundus in gastroptosis increases the difference in the level between it and the pylorus, and renders a greater amount of work necessary to lift the contents out of the stomach. Very remarkable dilatations sometimes follow laparotomy or develop in the course of acute infectious diseases.[60] The stomach becomes enormously distended within the course of a few hours. In some of these cases the dilatation apparently results from an acute obstruction in the duodenum, due to a kinking as noted above, and the motor insufficiency is especially apt to occur if the gastric wall has previously been diseased. Anomalies in the position of the stomach may also play a rôle.

(According to Mayo Robson[61] acute dilatation of the stomach is due to a paralytic condition of its wall which leads to an overdistention with gases and with excessive secretion, this in turn producing a kinking at the pylorus or at the duodenojejunal flexure. This is comparable to the intestinal obstruction occurring in a loop of paralyzed bowel which becomes distended with fluids and gases, and by its very weight causes a kinking of the intestine just below.—Ed.)

In other cases of gastric dilatation, no hindrance to the exit of food is apparent. Such dilatations have been met with in chronic gastritis, ulcer and carcinoma, in cases of hyperacidity and hypersecretion, and finally in association with enteroptosis, neurasthenia and diseases of the spinal cord. Possibly, certain cases of ulcer and hyperacidity occupy a peculiar position in the production of dilatation, in that the stenosis is functional and due to a pylorospasm.

The so-called atonic type of dilatation would present no interpretative difficulties were it not for the fact that dilatation is not always accompanied by a delayed emptying of the organ; on the contrary, indeed, the stomach may empty itself very slowly even though such a dilatation is absent, and conversely a dilatation may have no effect upon gastric motility. Conditions here are very similar to those observed in the varying behavior

of cardiac dilatation and cardiac efficiency. It is important to remember that an apparent dilatation does not necessarily mean an actual enlargement, for in conditions such as enteroptosis, it is difficult to estimate the size of the stomach. Nevertheless, gastric dilatation may occur with a normal emptying time,[62] in which case the only explanation possible seems to reside in a primarily lowered tonus of the fundus musculature, while the contractions occurring during digestion remain of normal strength. This condition is known as gastric atony.

Finally, gastric fermentation may cause a dilatation of the stomach. Fermentation is, of course, a common sequel to dilatation, yet in some instances it is primary. In Naunyn's cases,[63] dilatation and disturbances of gastric motility resulted from the introduction of large numbers of micro-organisms, together with easily decomposable food; and the dilatation disappeared as soon as the gastric contents were removed. The abnormal fermentation gives rise to large amounts of gas, which would, undoubtedly, interfere with the movements of the stomach. Possibly, also, the acid products of fermentation lead to a reflex spasm of the pylorus, comparable to that occurring with a hypersecretion of hydrochloric acid.

Effects of Motor Insufficiency.—The results of a motor insufficiency of the stomach may be very serious. In the first place, if the obstruction at the pylorus is nearly complete, the patient will die from lack of nourishment unless a communication be established by operative means between the stomach and the intestines. If the obstruction is incomplete, but sufficient to cause considerable stagnation, favorable conditions are present for the growth of micro-organisms, and the development of various abnormal decompositions. The presence or absence of free hydrochloric acid in the stagnated contents is an important factor in determining which micro-organisms shall develop and what shall be the character of the abnormal decompositions. As a rule, an atonic stomach absorbs material poorly, and the retention of digestive products (albumoses, etc.) in the gastric contents will interfere, to a certain extent, with the further progress of digestion. Possibly, also, abnormal quantities of true peptones are formed when the food remains in the stomach, and these cause a direct irritation of the gastric mucous membrane. Lastly, decomposed material and

large numbers of bacteria are passed on into the intestines, where they may irritate the more delicate membrane and initiate further abnormal decompositions.

Very remarkable nervous symptoms sometimes develop as a result of gastric dilatation.[64] Of these we may name the fully developed and rudimentary forms of tetany, epileptiform convulsions, tonic muscular contractions resembling tetanus, and, finally, symptoms of general depression and collapse. These symptoms usually occur in cases in which dilatation is associated with a hyperacid secretion, but the latter is not absolutely necessary. The cause or causes of these nervous symptoms are not well understood. One is tempted to assume that toxic substances are formed in the abnormal fermentations, and that these produce the symptoms by their action upon the nervous system. Indeed, French observers have prepared extracts from the stomach contents and have shown that they may give rise in animals to somewhat similar nervous disturbances. Yet these experiments need careful confirmation before much weight is to be attached to them. In some patients, no such poisons could be found; and Fleiner is of the opinion that mechanical causes, such as an overfilling of the stomach with a stretching of its parts, or perhaps the loss of fluids from the body, may play a more important rôle in the production of these symptoms.

Belching and Vomiting.—In addition to the normal movements of the stomach, others may occur which tend to empty its contents in the direction of the œsophagus. Waves of antiperistalsis have been directly observed in cases of gastric dilatation. (With the adaptation of the X-ray to gastric pathology, antiperistalsis has assumed an important place in the diagnosis of pyloric stenosis.[65]—Ed.)

By belching, we understand an expulsion of gas from the digestive tract through the mouth. Air in the œsophagus is easily expelled, for a powerful inspiratory movement with a closed epiglottis will draw air into the œsophagus which may afterwards be expelled during expiration. The gases may, however, come from the stomach, and they then consist either of air which has been swallowed, or of gases which have arisen from abnormal fermentations, *viz.*, carbon dioxide, hydrogen and methane. The gas frequently carries with it small amounts of liquid into the throat; and if this contains fatty acids, as it frequently does in

gastric fermentation, it gives rise to the burning sensation known as pyrosis. Hydrochloric acid itself may also be carried up and likewise produce unpleasant acid sensations.

The combination of movements by which the gas is expelled consists, on the one hand, of a relaxation of the sphincter at the cardiac end of the stomach, and, on the other, of a contraction of the abdominal muscles and diaphragm, whereby the intra-abdominal pressure is increased. Possibly, in some cases, the stomach also assists by contracting upon its contents. This complicated mechanism is most frequently set in motion by reflexes from the stomach or peritoneum.

In certain cases the same movements take the form of a clonic spasm, and this produces the condition known as hiccoughing. Hiccoughing is also incited by reflexes from the stomach and peritoneum, but it may furthermore arise from causes situated in the central nervous system, as is the case in the hiccoughing of hysteria and of severe lesions of the medulla.

Vomiting[66] is produced by a series of movements of the respiratory, abdominal and gastric muscles, which follow each other in a certain definite sequence, and which culminate in the expulsion of the contents of the stomach through the mouth. Vomiting is initiated by a deep inspiration, followed by a spasmodic contraction of the abdominal expiratory muscles, during which the glottis is closed and the diaphragm is held in a low position. The pyloric orifice is tightly contracted, the cardia is relaxed, and the stomach itself, though usually relaxed, may possibly perform antiperistaltic movements. During the primary deep inspiration some of the gastric contents are probably aspirated into the œsophagus, for the circular muscles of this tube are relaxed and its longitudinal muscles are contracted. When, finally, the abdominal muscles contract, the intra-abdominal pressure is greatly raised, and the contents of the stomach and of the œsophagus are expelled through the mouth.

This complicated mechanism is governed by a special centre in the medulla, situated not far from the respiratory centre. The "vomiting centre" may be acted upon directly by intracranial diseases and by poisons, or it may be stimulated reflexly through the vagus fibres from the stomach, especially from the terminations of those which supply the neighborhood of the cardiac orifice. Vomiting may

also be caused by reflexes from other organs, especially from the peritoneum, uterus, etc.

The act of vomiting not only affects the stomach, but also to a marked degree the general blood-pressure and the intrathoracic pressure. Traube has shown that at the beginning of the act the blood-pressure falls, and that the slow pulse is due to a vagus stimulation. Toward the end of the act both the blood-pressure and the pulse-rate are greatly increased. The salivation and the sweating which occur at the beginning of vomiting demonstrate how wide-spread are the changes incident to this act.

Sensations Arising from the Stomach.—A healthy man is not conscious of his stomach except when he is hungry or when the organ is overfilled. The sensation of hunger[67] is undoubtedly dependent to a great extent upon the condition of the stomach, though we do not know the exact changes which give rise to this sensation. It seems probable that the intestines also influence the sense of hunger, for patients with intestinal fistulæ have been observed whose hunger was not fully satisfied when food was put into the stomach, but was appeased if food material was also introduced into the intestines. The mental condition likewise influences the sensation of hunger, as is well known. To what extent the needs of the body for new material influence the sensation is still uncertain; yet these needs do seem to exert some influence, and the hunger of diabetes as well as that following muscular exertion seem to be examples of "tissue hunger." Of all these various factors that may influence hunger the condition of the stomach is the most important.

(Certain observers, Howell[68] among others, believe that no appreciable distinction can be made between hunger and appetite. Others, however, draw a sharp line between the two, defining hunger as the primitive, uneducated call for food, and appetite as the desire for food based upon previous pleasurable experience. According to Pawlow,[69] they differ also in their effect upon the secretion of gastric juice, hunger inhibiting the flow and appetite increasing it.

It is generally agreed that hunger is the psychic counterpart of a physical phenomenon evidenced by the so-called hunger contraction waves of the stomach. Boldyreff, who first recorded these in dogs, and Cannon and Washburn, who observed them in man, have described them as of periodic

occurrence with intervals of complete quiescence. Carlson,[70] on the contrary, believes that the stomach is never quiet and that the small, continuously occurring contractions increase in size and even become tetanic when the hunger state begins. These contractions may be recorded graphically by means of appropriate apparatus in individuals with gastric fistulæ, and in normal individuals during a period of fasting (Carlson).—Ed.)

Abnormally increased hunger is sometimes seen in patients with gastric ulcer or in those with hyperacidity, especially when there is an accompanying hypermotility of the stomach.

As a rule, however, gastric disturbances diminish the sensation of hunger, and the patient then has less inclination to take food (loss of appetite). Diminished hunger and loss of appetite are not precisely synonymous, for a person may say that he is hungry, and yet he will not eat, because he "has no appetite" for the food set before him. Loss of appetite accompanies many disturbances both of the gastric secretion and of gastric motility, but its exact cause is not known.

The sensations of fulness and pressure, which the healthy person experiences only after a full meal, become pathological if they are present when the stomach is not much distended. These sensations are produced more readily when the distention takes place rapidly than when it occurs gradually. This would seem to indicate that an increased tension of the stomach wall is an important factor in their production.

Gastric pain is frequently due to ulcerations of the wall of the stomach, whether these be round ulcers or are produced by carcinomata or by the action of corrosive poisons. It seems very probable that the pain in such cases is caused by the irritating action of the acid gastric contents upon the exposed base of the ulcer. Indeed, we know the acid may cause most intense pain, even when there is no ulceration. In such cases the pain may possibly result from a direct irritation of the terminals of the sensory nerves in the stomach wall; yet it seems more likely that, in most cases, it is due to a muscular spasm, more especially of the pyloric or the cardiac orifices. The sensation popularly known as cramps in the stomach may, therefore, in some instances be actually due to spasm of the gastric musculature. As we have said, such cramps are frequently caused by

hyperacid secretions, or by ulcerations. Gastric pains may, however, be of a neuralgic character; in this category belong some of the conditions called cardialgia. We are as ignorant concerning the nature of these as we are of neuralgias in general. The terrible pains which accompany the gastric crises of tabes and of other spinal affections are perhaps due to irritative-degenerative processes in the pneumogastric nerve. (In the tabetic cases, beneficial results have been reported following the severance of the sensory roots of the seventh to tenth dorsal nerves.[71]—Ed.)

Disturbances of the stomach may lead to a great variety of symptoms in other parts of the body. We have already mentioned the attacks of tetany and related symptoms. There may also be various vasomotor disorders, paræsthesias, neuralgias, migraine and vertigo, as well as disturbances in the innervation of the heart (irregular action) and of the lungs (cough). Some of these symptoms are of a reflex nature; others are probably due to poisons absorbed from the stomach. The investigation of this latter class of cases promises interesting results in the future.

(Another type of painful sensation that may properly be spoken of here is that called abdominal angina,[72] analogous, etiologically, to angina pectoris and to intermittent claudication. In this condition, the abdominal aorta and its branches are the seat of sclerosis, added to which there is usually the factor of vascular spasm. In addition to severe abdominal pain, these cases exhibit sudden and marked tympanites, constipation and sometimes renal disorders.—Ed.)

It is especially characteristic of the stomach that disturbances of its functions are combined in the most varied manner, and that one disturbance tends to bring others in its train. In certain cases it is possible to determine which of these is primary and which are secondary; in other cases, we cannot make such a separation.

Functional disturbances of the stomach are not accompanied by constant anatomical changes, and the condition known as gastric catarrh is especially destitute of any well-defined pathological-anatomical basis. The relation between functional and anatomical changes in the stomach is not easily studied, because so few gastric disorders are fatal and because the stomach changes so rapidly after death. For these reasons we know com-

paratively little about the relation between functional and anatomical changes in the stomach.

Not infrequently patients complain of loss of appetite, nausea and sensations of pressure in the abdomen, and yet the most careful investigations fail to reveal any secretory or motor changes. In a certain proportion of these cases it is possible that an unusual sensitiveness of the stomach exists, and that if the patients are careful in their diet they are relieved of the discomfort. In other cases, however, the symptoms seem to occur quite independently of the quantity and quality of the nourishment, and to depend rather upon the psychic state of the individual. To this class of cases Leube has given the name of nervous dyspepsias. The frequency of the latter increases as the resistance of people to the unpleasant things of life diminishes. We all know the great influence the mind exerts upon the digestion, and it is easy to conceive that this influence might be pathologically intensified in neurotic individuals. Indeed, secretory and possibly even motor functions of the stomach may be thus affected. Strümpell has termed such cases psychic dyspepsias. Dreyfuss,[73] who has given this subject especial attention, has found the chief predisposing conditions to be an inherited or acquired neuropathic disposition, epilepsy, hysteria and circular insanity.

Disturbances in the Secretion of Bile[74]

We know little of the variations which diseases cause in the amount and composition of the bile. Physiological experiments would seem to indicate that the amount is diminished in all those conditions in which but little food is taken. This diminution affects especially the water and the bile salts; but we are less certain as to the effect of inanition upon the bile pigments, for considerable variations in these occur normally.

Substances not ordinarily present may appear in the bile. Thus when the sugar in the blood exceeds 0.3 per cent. it is excreted by the liver, and the same is true of other substances, among which the antiseptics may prove of practical significance. Albumin appears in the bile at times, *e.g.*, after the use of alcohol. The secretion of pigments may be diminished, as happens in some instances of degeneration of the hepatic cells during infectious diseases. The pigment content is high in passive hyperæmia

of the liver; while in numerous conditions it undergoes considerable variations.

It is possible to affect the composition of the bile through changes in the blood. When large numbers of red blood-corpuscles are destroyed, the liberated pigment is taken up by the various organs, especially by the liver (p. 116). This directly influences the bile. Its quantity is at first diminished, the formation of the pigments from the hæmoglobin is increased, and the bile salts are either normal or are diminished. Not infrequently the oxyhæmoglobin itself passes into the bile, even long before it appears in the urine.

The composition of the bile is affected also by certain poisons, among which are toluylendiamin, arseniuretted hydrogen and phosphorus. The first two destroy the red corpuscles of the blood, but phosphorus does not do so in mammals. In the earlier stages of intoxications with these compounds, the total quantity of the bile is usually diminished, the pigments are increased, and the bile salts only slightly increased or even considerably diminished. Owing to an increase in its content of nucleoproteids, the bile becomes thick and viscid. In the later stages of these intoxications, the bile increases in quantity, its composition varying in different ways. These quantitative and qualitative changes are produced in part by the destructive action of certain of these poisons upon the red blood-corpuscles. Yet this is not the only cause of the biliary changes. The main factor seems rather to be a stimulation of the liver cells to the production of an abnormal secretion.

Gall-Stones.—Gall-stones[75] usually originate in the gall-bladder. At times only one stone is found; more frequently, however, several or many are present. The numerous calculi so frequently found in the gall-bladder at autopsy are in many instances all of about the same size. In other cases, they occur in groups as, for example, one or two large, ten or twelve medium-sized and fifty or more tiny stones. Such have been termed generations of gall-stones. The explanation for this grouping of stones seems to be that during some pathological process in the past several nuclei originated, and that when once started the stones tended to act as centres about which the bile constituents were deposited. This continued until some change in the conditions in the bladder allowed a fresh set of stones to start.

Gall-stones are composed, for the most part, of cholesterin and of the calcium salt of bilirubin. Both these substances usually enter into the composition of the stone, but some stones are formed entirely of one or the other of them. Other materials which may be present in biliary calculi are calcium carbonate, salts of the heavy metals, pure bile pigments and derivatives of these pigments.

The calcium salts probably arise, for the most part, from the epithelial cells of the biliary passages, their amount being independent of the diet. This is true also of the cholesterin, which is dissolved in the bile through the agency of cholates, soaps and fats. These solvents may hold far greater amounts of cholesterin in solution than ever occur in the bile.

Under certain conditions, nevertheless, bile preserved aseptically may spontaneously precipitate cholesterin crystals. It is possible that desquamated epithelium favors this process. There is no difficulty, therefore, in understanding how cholesterin stones may arise if conditions, such as tight-lacing, pregnancy, etc., are present, which predispose to the stasis of bile. According to Aschoff the cholesterin stone showing radiating lines is the result of a sterile breaking up of bile. This concrement usually occurs singly, grows slowly and has an uneven surface corresponding to veins of crystallization of varying length. Its chemical structure speaks for a normal bile, not for one changed by inflammatory processes. All other types of stone—and these comprise the majority—arise on an infectious basis.

The normal bile of a healthy individual is generally sterile, despite the free communication between the biliary and intestinal tracts.[76] This is to be attributed to the constant movement of the bile which sweeps before it all alien bodies, even micro-organisms which have been artificially introduced.[77] Ligation of the common duct, however, and the consequent bile stagnation, permit of a ready growth of bacteria. Indeed, in animal experiment, the mere ligation of the duct will cause infection of the bile. In this case, the micro-organisms probably enter the biliary tract from the intestines, despite the ligature.

In certain infections, notably typhoid fever and pneumonia, the bile frequently contains micro-organisms.[78] It is probable that in the case of the colon bacillus, infection has

occurred via the bowel; while with the typhoid bacillus, particularly, the source is hæmatogenous. French observers pointed out many years ago the frequency of cholangitis and cholecystitis as sequelæ of typhoid and paratyphoid infections, and to this we fully subscribe.

The bacterial infection produces an inflammation of the mucous membrane and a desquamation of its epithelial cells. These latter contain undissolved cholesterin. They likewise contain calcium salts, and these probably react to form the insoluble calcium salt of bilirubin. From this salt, as well as from the amorphous cholesterin in the cells, the biliary calculus takes its origin. Its further growth is carried on by the deposition and recrystallization of new material, especially of cholesterin.

Several facts favor the view that gall-stones result from infectious catarrhs of the biliary passages. Thus, bacteria may be recovered from the centres of gall-stones, although this is possible only in the minority of cases. Gall-stones have also been produced experimentally by causing biliary stasis and by infecting the bile-passages with bacteria of low virulence.[79] As we have already stated, groups of stones in a gall-bladder are frequently of about the same size and presumably of the same age, and it may be inferred that they have all originated at about the same time from a common cause. Infection of the bile-passages is by no means an infrequent event after certain infectious diseases, especially after typhoid fever, and it is quite conceivable that this furnished the common cause for the formation of a number of stones, and that afterwards the bacteria died out of the bile and no new stones were formed. In other cases, typhoid bacilli live for years in the gall-bladder and pass thence at periods into the intestines, to leave the body along with the fæces. Here the conditions for a continued new formation of stones are present.

Cholelithiasis frequently produces no symptoms; and especially is this so when the calculi lie quietly in the gall-bladder without occluding any of the ducts. Gall-stones may, however, give rise to severe pains, as well as to inflammations, peritoneal adhesions, perforations and septic infections of the liver. All of these evil consequences are initiated by an inflammation of the gall-bladder containing the stones. Riedel believes that this inflammation may be induced merely by the presence of the stone,

which acts as a foreign body, but that in some cases, at least, it is started by a traumatism. The cystic duct is then likely to become occluded either by the extension of the inflammation to its mucous membrane or by the lodgement of a stone within it. Hydrops of the gall-bladder ensues. Its original contents of bile become modified by interchange with the lymphatic fluids. The cholates early disappear, the pigments follow them, and finally a clear fluid is left, which contains salts, cholesterin, nucleo-albumin and characteristic proteids. If bacteria are present they may cause suppuration. The inflamed wall of the gall-bladder may ulcerate, it may become adherent to surrounding structures or it may perforate. Not infrequently the stone passes through the cystic duct and occludes the common duct. It may then produce a variety of inflammatory processes in the liver, the peritoneum, the stomach and the intestines.

The stagnation of bile and the injury to the walls of the biliary passages—both common results of gall-stones—greatly favor the development of secondary infections, both enterogenous and hæmatogenous, via the portal vein. The obstruction caused by the stones is conducive to the multiplication of bacteria which have thus entered the bile, and inflammatory processes of all kinds result.

Carcinomata sometimes complicate gall-stones, and in such cases it is supposed that they are caused by the irritation of the mucous membrane. Indeed, carcinoma of the bile-passages arises almost exclusively on the basis of cholelithiasis.

Biliary colic is the most feared manifestation of gall-stones. It is characterized by attacks of violent pain in the region of the liver and is usually accompanied by vomiting and fever and sometimes by jaundice. The paroxysm may last for hours or days. The colicky pains are caused by the inflammation and distention of the tract and by the spasmodic contractions of the muscle in the gall-bladder and ducts. In a certain number of cases the attack is precipitated by the passage of a small stone from a wide into a narrow passage, as happens at the exit from the gall-bladder, or just before the entrance into the duodenum. Yet such is not always the case. A gall-bladder which contains large stones, and which is isolated by an old occlusion of its duct, is not infrequently the seat of colic. Indeed, colic may come from a gall-bladder which contains no stones and which is

merely shrunken and surrounded by adhesions. The immediate cause of the paroxysm of biliary colic, not only in these exceptional cases, but possibly in all, is an inflammation of the bile-passages. This may either drive the stone into a narrower portion of the duct, or it may cause the mucous membrane to swell about the stone, thus occluding the passage. The fever and jaundice that so often accompany biliary colic will be discussed in another place (p. 266).

The Exclusion of Bile from the Intestines.—The bile may be excluded from the intestines by gall-stones lodged in the common or hepatic ducts, by tumors growing within them or pressing upon them from without, or finally by catarrhal inflammations which cause a swelling of the mucous membrane, and so occlude the narrower portions of the passages, especially the exit of the common duct at the papilla of Vater and the smaller bile capillaries within the liver.

The effect of an occlusion of the common duct varies with the site of the obstruction. If the latter be seated high up, bile alone is excluded from the intestines; whereas, if it be at the papilla of Vater, the pancreatic juice may also in part or altogether be shut off. Experiments upon dogs have shown that when no bile can enter the intestines the digestion and absorption of proteids and carbohydrates proceeds approximately in a normal manner, whereas the absorption of fats is seriously interfered with; only about forty per cent. of the fat taken in the food being absorbed, as compared with the normal of ninety per cent. Fr. Müller[80] has shown that the same relations hold good for man. If bile be excluded from the intestines, the absorption of carbohydrates is not affected and the absorption of proteids is only slightly lessened; while, on the other hand, from sixty to eighty per cent. of the fat taken in the food escapes absorption as compared with the normal of from seven to eleven per cent. The "clay color" of the stools in these cases is caused partly by the absence of bile pigments and partly by the presence of excessive quantities of fat. It is difficult to explain the cause of this diminished absorption of fat on the theory that the latter is taken up from the lumen of the intestines as fine particles. If, however, we assume that it is absorbed in a state of solution after having undergone hydrolytic cleavage,[81] then the important rôle

played by the bile might in part be explained by the fact that the cholates are capable of holding large quantities of fatty acids in solution.[82]

(Hewlett[83] has shown that the bile may assist the digestion and absorption of fats in other ways. In the first place, the emulsification of fats is favored by the presence of bile; and in the second, the bile accelerates the fat-splitting action of the pancreatic juice eightfold and even more. There appears, therefore, to be a sufficient physiological explanation for the effect which follows an exclusion of the bile from the intestines.—Ed.)

Even though the bile be excluded from the intestinal tract, it is possible to maintain nutrition by paying sufficient attention to the diet, which should, under these circumstances, consist mainly of proteids and carbohydrates. If the food contains much fat, the latter undergoes excessive cleavage through the action of the pancreatic juice and of the intestinal bacteria. The products of this decomposition irritate the intestinal mucous membrane and may lead to disturbances of its functions. For this reason the administration of fats to patients with biliary obstruction is not only useless but frequently injurious. We are not yet certain what effect the absence of bile exerts upon the bacterial decompositions which normally take place in the intestines. The putrefaction of proteids[84] has been found to be increased in some instances, while in others it has been diminished. It is very doubtful if the bile exerts any antiseptic action upon the growth of micro-organisms in the intestines, for Strasburger[85] found no increase, and even a diminution, in the number of bacteria in the fæces in cases of complete biliary obstruction. Possibly, however, the absence of bile allows the intestinal decompositions to pursue an abnormal course.

Jaundice.—If the lumen of the common duct be obstructed, and if the liver cells continue to secrete bile, the gall-bladder and the bile-passages become filled with the secretion, the pressure of the bile within them increases, the liver cells are forced apart, and the bile is absorbed into the lymphatic system or directly into the blood.[86] It thus enters the general circulation and permeates all the organs of the body. The liver cells may, indeed, resecrete some of the constituents out of the blood; yet this has little effect,

for, the passage into the intestines being obstructed, these constituents are again reabsorbed.

In jaundice, the bile pigments are deposited in various tissues, and the skin assumes a color which varies from a light yellow to a dark green or brown. Whether these different shades are due to a blending of varying amounts of bile pigments with the color of the skin, or whether they arise from a conversion of bilirubin into other pigments, has not been decided. The jaundice may be visible within a few hours after the obstruction has taken place, though usually it does not appear for from one to three days. The retained bile pigments are excreted by the kidneys and by the sweat-glands; but they do not, as a rule, appear in the tears, the saliva or the gastric juice.

Of the constituents of the bile which pass into the lymph and the blood, the bile salts are of especial interest on account of their known toxic properties. During the first few days of jaundice they can frequently be detected in the urine, but in the later stages they are usually absent. Concerning the quantitative relations of other constituents of the bile—to what extent they are formed, to what extent eliminated in the various secretions, and to what degree destroyed in the body—we know but little.

Jaundice may arise not only from an obstruction to the flow of bile through the larger passages, but from obstructions located in the smaller biliary capillaries. These produce the jaundice which may accompany various diseases of the liver, such as cirrhosis, carcinoma, cholangitis and calculi of the finer ducts. The "biliary thrombi" described by Eppinger are a fruitful cause of such obstructions. The development of jaundice is dependent less upon the nature of the disease than upon its location, the essential factor being an obstruction to the exit of bile. The jaundice that so frequently accompanies gall-stones may be due to the lodgement of a stone in the common or hepatic ducts, or to an associated inflammation of the mucous membrane. According to Riedel, the latter is the more common.[87] Closure of the cystic duct does not ordinarily cause jaundice.

The resorption of the stagnating bile is influenced not only by the degree of mechanical obstruction, but also by the consistency of the secretion. A thick viscid bile, rich in pigments, may be reabsorbed even when the obstruction is a comparatively slight one, such as might be caused, for example, by a catarrh of the

bile-passages, by a biliary thrombus or by the swelling of liver cells which have undergone fatty degeneration. The icterus of phosphorous and of toluylendiamin poisonings is usually produced in this manner,[88] as is that which may accompany snake-bites, pneumonia, pyæmia, septicæmia and various other intoxications and infections. In none of these can a marked obstruction to the outflow of bile be demonstrated. This fact gave rise to the theory that the jaundice in such cases does not depend upon the changes in the liver, but upon the formation of biliary pigments in other parts of the body. It is, indeed, possible for bilirubin to be formed outside of the liver, for this happens in old blood-clots; yet the amount thus formed is very small and never produces jaundice. Indeed, we may say that, so far as we know, jaundice is always of hepatic origin, and that we have no proof that a hæmatogenous type can occur.

Conditions are particularly favorable for the resorption of bile when the biliary capillaries are narrowed by catarrh. Thrombi in the bile-passages, upon which Eppinger has laid emphasis, are especially prone to occur when the composition of the bile is altered by abnormal conditions of secretion. Such an alteration is frequent; indeed, even fibrinogen may appear in the bile-ducts. The occurrence of these thrombi may well explain, on a mechanical basis, some of those difficult cases of icterus—in phosphorous poisoning, hæmolytic conditions and in the infectious diseases—which give no evidence of a gross obstruction to the flow of the bile. It must be admitted, however, that this conception of a mechanical obstruction is in some cases based upon purely hypothetical considerations. The question here resolves itself into a study of the conditions under which the liver cells might pour their secretions directly into the blood or lymphatic systems, rather than into the bile capillaries.[89] A better understanding of the part the parenchyma cells play in these processes would possibly throw considerable light upon this vexed problem.

The etiology of the so-called **catarrhal icterus** is but little understood. The view formerly held was that of Virchow, who looked upon the duodenal catarrh with an occlusion of the papilla of Vater by a mucus plug as the underlying cause. But the observation of Eppinger[90]—the occlusion of the common duct as a result of the swelling of its lymphoid tissues—shows what

variable factors may be present. My clinical experience has led me to believe more and more that this form of jaundice is generally due to changes in the liver cells, rather than in the bile-passages, in other words that we have to do with a hepatitis.

The cause of **icterus neonatorum** which occurs in about sixty per cent. of all new-born children is not well understood.[91] This much is certain, that it results from the resorption of bile; for not only the pigments, but the bile salts as well, are found in the various body fluids. It seems probable also that icterus neonatorum is associated with a destruction of the red blood-corpuscles, for it is especially apt to develop in those infants who have had the cord tied late and who have received, therefore, a larger amount of blood from the placenta. We know that jaundice frequently accompanies an increased destruction of red blood-corpuscles, as happens in paroxysmal hæmoglobinuria, but the attempts to produce it experimentally by the introduction of hæmoglobin have hitherto failed. There seems, therefore, to be some other factor present than the mere destruction of the erythrocytes. Possibly, as Quincke believed, the jaundice of the new-born is due to the resorption of bile from the intestines. This theory receives some support from the fact that for several days after birth the blood from the intestines may not go through the liver, but may pass directly into the general circulation from the portal vein by way of the ductus venosus. An infectious origin has also been suggested (Czerny and Keller).

(Considerable attention has lately been devoted to another form of icterus, the so-called hæmolytic icterus.[92] Two types are recognized, the congenital and the acquired. In both there is an acholuric jaundice with urobilinuria and splenomegaly. A striking feature of the congenital type is the evidence of a diminished resistance of the erythrocytes to hypotonic salt solutions; while in the acquired form the fragility of the (unwashed) corpuscles does not vary greatly from the normal. The blood-picture of the acquired type may in some cases closely resemble that of pernicious anæmia. This form of jaundice is of particular interest in view of the therapeutic success, reported by many observers,[93] of splenectomy.—Ed.)

Effects of Jaundice.—The obstruction to the flow of bile may

cut off this secretion from the intestines with the results which have already been described (p. 266). On the other side, the liver cells are affected. They become compressed and separated; and, though for a time they may continue to perform their functions normally, nevertheless, after a while, they suffer both in structure and in function. Areas of necrosis and inflammation may appear. These are due in part to the toxic action of the bile itself, and, in part, to the infections that are so prone to appear in stagnating bile. It is impossible to apply the experimental data upon this subject to man, because the various animals differ so greatly in the effect produced by a stasis of bile upon the liver.

It is difficult to decide which constituents of the bile produce each of the varied general symptoms of jaundice. The cholates seem to be the most toxic in their action, although recently attention has been directed to the poisonous properties of the biliary pigments.[94] The itching of the skin so frequently present is apparently due to the deposit of pigment in the skin. In the early stages of jaundice the heart's action may become slow and irregular, both in force and frequency, and the blood-pressure may fall (see p. 60). These symptoms seem to be due to the action of the bile salts, for even small doses of sodium cholate stimulate the central endings of the vagus nerve, and larger doses act upon the heart itself. The convulsions that very rarely occur in the beginning of jaundice are also possibly due to the action of the bile salts, for the injection of very large amounts of cholates will produce convulsions. True cholate intoxication occurs in man only when the obstruction to the outflow of bile is complete or nearly so, and when the formation of these salts is not materially interfered with. It may accompany catarrhal jaundice, cholelithiasis and carcinomatous obstruction. Yet the cholate symptoms are by no means always present in jaundice, and often they last only a short time; for the quantity of bile salts in the blood varies enormously and it is usually small in the later stages of an obstruction.[95] This is due apparently to the fact that the hepatic cells may lose their ability more or less to produce the bile salts, as well as to the constant endeavor on the part of the liver to remove bile salts from the blood. For these reasons there are frequently no signs of cholate intoxication even when the jaundice is most profound.

Other Hepatic Toxæmias.—At times serious toxic disturbances develop in the later stages of liver disease, and these may or may not be accompanied by jaundice. The patient becomes stuporous and delirious, and after a few days of high fever and perhaps convulsions, death usually closes the scene. The condition resembles the termination of certain other metabolic diseases, such as the coma of diabetes and the uræmia of nephritis. It is very improbable that these late toxic symptoms are in any way caused by a resorption of bile, for, in the first place, the picture differs from a cholate intoxication in the high fever and in the frequency of general convulsions; and in the second place, diseases of the liver may terminate in this manner even though hardly any jaundice is present, and even though, furthermore, on account of the extensive destruction of hepatic cells, it is probable that only very small quantities of the bile salts are manufactured.

A wide-spread degeneration of the liver cells seems to be the underlying cause of these toxæmias. The hepatic cells are known to perform very important metabolic functions, such as the storing of carbohydrates, the formation of urea out of ammonium salts, the conversion of toxic aromatic compounds into the comparatively harmless ethereal sulphates, and the disposal of various other poisons absorbed from the intestines. It may, therefore, be easily understood how seriously the metabolism might suffer when the liver is thrown out of function. Possibly the above toxæmias are caused by poisonous compounds which would normally be rendered non-toxic in the liver. Of great interest in this connection is the fact that geese will frequently die of convulsions after extirpation of the liver, if they are fed on a rich nitrogenous diet.[96] The same holds true for dogs if an Eck fistula between the portal vein and the inferior vena cava permits the blood to flow from the intestines directly into the general circulation without traversing the liver, under which circumstances the liver cells gradually degenerate. Certain symptoms presented by these animals would seem to be due to the action of the carbamic acid. If ammonium carbamate be injected into the portal blood of normal animals, it is converted into urea in the liver. In animals from which the liver has been extirpated or thrown out of function this does not occur, and in them the carbamic compounds would be free to produce toxic symptoms.

The toxæmia associated with extensive hepatic disease may

also possibly be due to the formation of poisonous compounds from the disintegrating liver cells. Finally, some of these intoxications are undoubtedly of infectious origin, as is probably the case in acute yellow atrophy and in the not infrequent infections of the biliary passages which follow chronic obstruction.

Considerable attention has been given in recent years to the factors governing the appearance of urobilin (hydrobilirubin) and its forerunner, urobilinogen, in the urine and in the fæces.[97] Urobilinogen is derived from bilirubin by the reducing action of the intestinal flora. In man, urobilinogen and urobilin are formed exclusively—or at least predominantly—in the intestinal tract; whether they may arise in the liver also, as in dogs, is not improbable, though not confirmed. From the intestines, hydrobilirubin passes into the circulation and is excreted in part by the kidneys as urobilin. Normally, then, urobilin and urobilinogen occur in the urine, but in negligibly small amounts. The greater part of the urobilin thus absorbed from the intestines is returned to the liver, and passing once more into the bile, again reaches the bowel.

In many hepatic disorders, this intermediate urobilin circulation is disturbed. The urobilin returning to the injured liver cells is no longer excreted by them into the bile, but is thrown into the lymph and blood and is then excreted by the kidneys in large amount. Urobilinuria may, therefore, be regarded as the best and most constant clinical index of a disturbed liver function. (Unlike alimentary galactosuria, however, it is not significant of particular hepatic derangements—cirrhoses, catarrhal icterus—but may occur in any condition deleteriously affecting the liver function, *e.g.*, cirrhosis, passive hyperæmia, malignancy and even parenchymatous degeneration accompanying the acute infections (Bauer).[98]

It is evident from what has been said concerning the formation and circulation of urobilin, that in complete closure of the common duct, no urobilin can be formed because no bilirubin reaches the bowel. In these cases, the absence of the former in the urine and fæces speaks for a complete, as against an incomplete, occlusion of the duct.

The same is true in practically every respect of urobilinogen, which is readily oxidized into urobilin by a brief exposure to light and air and is, therefore, not so accessible to study. In hepatic

insufficiency—when the common duct is patent—it may be demonstrated in freshly voided urine by the Ehrlich aldehyde reaction or by means of the spectroscope.—Ed.)

The Pancreatic Juice

The complete exclusion of the pancreatic juice from the intestines without a concomitant exclusion of bile is extremely rare, for the gland usually possesses two functioning ducts.[99] A closure of both of these is uncommon; and a total degeneration of the secreting glandular parenchyma is likewise very exceptional. By far the most frequent site of a pancreatic obstruction is the papilla of Vater, and here not only the duct of Wirsung, but the common bile-duct would be closed. One can never be certain to what extent the pancreatic juice is diminished when the duct of Wirsung alone is occluded, because the secretion still finds an exit via the duct of Santorini.

For these reasons we are insufficiently acquainted with the results of a simple exclusion of the pancreatic juice from the intestines. F. Müller[100] studied the fæces of several patients who had extensive pancreatic degeneration, and found that the absorption of carbohydrates in the digestive tract was not at all affected by the disease, that the absorption of the proteids was only slightly affected, and that the total quantity of fats absorbed was likewise not far from the normal. The cleavage of fats in the intestines, however, was considerably diminished; for, of the fat in the fæces, only forty per cent. was found to be split into fatty acids and soaps, as against the normal of about eighty-four per cent. These figures correspond well with those obtained in animals with ligated ducts. (Other observers, however, have come to different conclusions both as to amount of fat absorbed from the intestines in pancreatic disease and as to the extent of cleavage. The variations in observations relative to cleavage are due probably to differences in the type of fat ingested—whether emulsified or not—and to individual differences in the fat-splitting power of the stomach.[101]—Ed.) Müller's results, too, would be more significant, had he been able to make more extended observations on the amount of fat utilized, particularly when larger amounts of fatty food were ingested.

(A greater part of the pancreas may be rendered functionless,

experimentally, or by such conditions as extensive cirrhosis, carcinoma, softening or even by an apparently complete closure of the main excretory duct by stones, without the appearance of digestive anomalies. This is due in all probability to the vicarious action of the succus entericus, the bile and the gastric juice, and to the patency of the accessory pancreatic duct. But when the loss of function is complete, certain changes in the fæces manifest themselves which have a practical value in diagnosis. Thus, characteristic of severe pancreatic lesions are large fatty stools—not acholic, however, as in complete biliary obstruction; further, the predominance, as a rule, of neutral fat in these stools; the presence of large amounts of undigested muscle fibres, only about one-half of the ingested proteid being utilized; the persistence of the nuclei in muscle fibres taken in the food, the gastric juice not having the power to digest nuclei; and finally, the evidence of putrefaction and sometimes of fermentation.[102]—Ed.)

The experimental studies of Abelmann have demonstrated the serious impairment of absorption which follows the extirpation of the pancreas of animals. About fifty-six per cent. of the ingested proteids, twenty to forty per cent. of the carbohydrates and all of the non-emulsified fats appeared in the fæces. Of the latter, from thirty to eighty-five per cent. had undergone cleavage into fatty acids and soaps. If the fat were introduced in the form of a natural emulsion, such as milk, a considerably larger proportion—about thirty to fifty per cent.—was absorbed by the intestines. Other experimenters have obtained quite different results;[103] in many cases the fat was not absorbed at all, and in others up to eighty per cent. was absorbed. It seems to me that the results of these experiments cannot be applied directly to human pathology, for extirpation of the pancreas is attended with considerable shock to the animal and we have no data as to how the secretion of bile is influenced by these operations. Furthermore, the internal secretion of the pancreas plays a significant part in these processes, particularly in that of fat absorption. Possibly the entire resorptive power of the intestinal mucosa is regulated by this secretion[104] (see chap. VII).

Fat Necroses.—Attention must be directed further to a severe

picture which may result from the extravasation of pancreatic juice into the peritoneal cavity. This may be due to trauma; while in other cases there is no evidence of injury, but instead a back flow of bile into the duct of Wirsung, such as occurs, for example, when the papilla of Vater is blocked by a stone. The pancreatic juice activated by the bile or intestinal secretions causes an auto-digestion and necrosis of the gland, and leads to a destruction of the fatty tissue, not only about the pancreas, but often in the entire abdominal cavity and even in the pleural cavities. This condition was first described by Balser[105] under the name of fat necrosis.

The fat in the neighborhood of the pancreas assumes a peculiar light, opaque appearance due to its decomposition into free fatty acids and fatty acid salts, particularly those of calcium.[106] These necrobiotic changes lead in turn to a melting away of the tissue, and to the formation of abscess-cavities which are filled with necrotic material.

Fat necroses may be produced experimentally by plugging the pancreatic arteries, by the injection of oil, bile or intestinal juice into the pancreatic ducts, by the introduction of activated trypsin into the ducts, by the implantation of a normal pancreas into the abdominal cavity of a healthy animal and finally by allowing the pancreatic duct to pour its contents into the free abdominal cavity. Both the necroses and fatal outcome in the implantation experiments may be prevented, however, by a preliminary immunization of the animal with trypsin.[107]

The clinical picture in animal experiments involves complex factors. Fischler[108] showed the important rôle of the liver in these particulars. Animals with an Eck fistula, for example, are extremely sensitive to lesions of the pancreas; a mere handling of, or pulling upon, the gland, which ordinarily have the effect of producing only slight areas of necroses, and are borne with impunity by a healthy animal, cause in those with the fistula a severe set of disturbances. A very characteristic central necrosis of the liver lobules occurs coincident with the appearance of the lime salts of the fatty acids in the liver cells. The animal dies in twelve to thirty-six hours with severe nervous manifestations. On the other hand, if there has been a previous immunization with trypsin, these liver changes do not appear and the

animal survives. This is further evidence of the chemical relationship existing between the liver and the pancreas.

The clinical manifestations are variously explained on the basis of an intoxication with trypsin, with the substances arising in the necrosis of the pancreas, with soaps and with the split-products of the ferments set free in the process.[109]

The Processes in the Intestines

The Effect of Poisons Upon the Intestines.—The intestines may be injured by various substances, such as the fatty acids, the metallic salts, aromatic compounds, etc. Many of these are used therapeutically, while others may be taken in the food. It is not easy to separate those which are toxic from those which are not, for the susceptibility of different individuals varies enormously in this respect. Even such a marked poison as arsenious acid, which in most men causes a violent enteritis, may become comparatively harmless through habituation; and quantities may then be borne which would ordinarily be almost immediately fatal.

Toxic substances may be elaborated outside the body by the action of bacteria. These include the so-called ptomains,[110] many of which, such as neurin, mydalein and mytilotoxin, are extremely poisonous. Since such compounds are formed only in the later stages of putrefaction, an intoxication from this source is most apt to follow the ingestion of decomposed food. Specific toxins, formed by specific bacteria, *e.g.*, the anaerobic bacillus botulinus, may also be introduced with the food. Some of these poisonous substances injure the wall of the intestines, producing anatomical and functional disturbances, while others are absorbed and produce more general symptoms. It is often difficult to determine whether a certain intoxication resulted from poisons introduced with the food, or whether it arose from toxins which were produced within the intestines by the abnormal action of bacteria; yet in some instances the former is by far the more probable, for the symptoms appear almost immediately after the ingestion of the decomposed food. The same is also true when the intoxication is caused by material which has been cooked, such as meat, fish, sausage, oysters and eggs, for it is then very improbable that any living organisms other than spores were introduced.

Abnormal Bacterial Processes within the Gastro-Intestinal Tract.—Numerous bacteria are regularly carried into the stomach with the food. A portion of these are there destroyed, some are reduced in virulence, and a part pass on but slightly injured into the duodenum. Of these, some decompose the carbohydrates and split the fats, thus producing organic acids, such as acetic, lactic and succinic acids, even in the small intestines. In the lower ileum, and especially in the colon, the bacterial decompositions normally become more marked, and here the putrefaction of the proteids is a normal process.

The number of bacteria in the human intestines varies greatly.[111] The dried fæces of a healthy man are made up of one-eighth to one-fourth, by weight, of bacteria. Yet the upper small intestines in fasting animals, at least, are almost free from micro-organisms, which would seem to indicate that they regulate their bacterial flora to a marked degree.[112]

Certain factors apparently inhibit bacterial growth in the small intestines. As we have seen, the hydrochloric acid of the stomach diminishes the number of bacteria present in the food, and it is probable that the bile acids, the fatty acids produced by cleavage of the fats, and the intestinal secretions exert a certain antiseptic action in the upper intestines. The living epithelium itself possesses bactericidal power; while, according to certain observers, the feebly bactericidal succus entericus is rendered more potent, *in vitro* at least, by the pancreatic juice. Of greater importance, however, is the rapid transit of material through the duodenum and ileum, for the few hours that food remains there do not allow sufficient time for the bacteria to multiply. Fortunately, in the large intestines, where the transit is slower and where the bacterial action is most marked, the greater portion of nutritive material has already been absorbed, and the bacteria find less to decompose.

Another protection against the growth of strange bacteria in the intestines is the inhibitory action which the normal flora seems to exert upon the growth of outsiders.[113] For this reason, the normal flora of the intestines is probably very useful. Whether it is absolutely necessary or not, is a question that has received different, though not irreconcilable, answers from different investigators.[114] Guinea-

pigs may be reared upon sterilized milk; whereas chickens do not thrive on bacteria-free food—an observation which would appear to support the view that the presence of micro-organisms in the gastro-intestinal tract is necessary during extrafetal life. In man, at least, the intestinal bacteria are important in the digestion of cellulose, upon which the ordinary enzymes do not act.

Whatever the importance may be of the intestinal flora in the digestion and absorption of food, it is probable that these micro-organisms are of great, perhaps vital, significance as protective forces against the invasion of alien bacteria. To this we have already referred (p. 156).

The kind of micro-organisms in the intestines depends partly upon the food taken, and partly upon the condition under which the individual lives.[115] The intestinal contents of a new-born infant are sterile, but after birth they quickly become infected, and at the end of the fourth day a fully developed intestinal flora is present. The latter varies with the kind of food used—whether mother's or cow's milk—and further with each change in the food in later life. Upon this phenomenon are based the attempts that have been made to expel certain flora from the bowel by altering the diet.[116]

So long as the epithelium remains intact and healthy, the body is fairly well protected from invasion by the bacteria which happens to be present in the intestines.[117] The epithelial cells form a protective bulkhead, their antibacterial action being attributed by some authors to their content of nucleinic acid and its combinations, substances which are acid in reaction and will cause a precipitation of proteids.[118] Yet the protection afforded to the body by the intestinal mucosa is not an absolute one. Apparently the tubercle bacillus may penetrate the intact mucous membrane, and slight lesions will certainly render the epithelium permeable to many bacteria.[119]

The soluble products of bacterial action frequently pass through the normal mucosa and in so doing they may possibly render an important service to the individual by immunizing him against the action of the bacteria from which they are derived. These toxins, which are of a proteid nature, may in many cases be digested in the intestines, just as are other proteids; yet it would appear that this does not occur in the intestines of in-

fants.[120] Antitoxins penetrate the epithelium only when dissolved in homologous milk.[121]

Many intestinal diseases, perhaps the majority of them, are due to abnormal bacterial action within the intestines. The bacteria ordinarily present may increase in number or in virulence, or bacteria that are not usually present may give rise to pathological changes. Such foreign micro-organisms must, of course, be introduced from without; thus it is manifestly impossible, for example, to acquire cholera at a time when no cholera bacilli are about. Yet it is often extremely difficult to be certain of the absence of pathogenic germs in a certain locality, for individuals, not themselves ill, may harbor and distribute virulent bacilli (*e.g.*, from chronic typhoid infections of the bile-passages or urinary bladder). The mere introduction of pathogenic bacteria does not necessarily do any harm; for just as large numbers of harmless bacteria daily enter the gastro-intestinal canal and there disappear, so may pathogenic organisms be destroyed without their producing any ill effect. They succumb to the various protective agencies in the stomach and intestines that have already been described. In some cases, however, the bacteria introduced are so numerous or so virulent that they cause the disease in practically every individual in whom they enter, as is illustrated by the fact that every person who has partaken of a particular dish may become ill. Possibly, aggressin-like bodies are present in an infected food.

It is often impossible to say in what manner the infection has taken place, whether it is by overcoming the normal inhabitants of the intestines, or by causing a lesion of the mucosa, etc. Apparently different factors enter into consideration in different infections. We know, for example, that the cholera vibrio is extremely sensitive to the acid reaction of the gastric juice; and clinical experience has shown that the disease is especially apt to attack individuals who have presumably a lessened gastric acidity, caused either by some slight digestive disturbance or by great fear of contracting the disease.

Intestinal indigestion is apt to be produced in some individuals by certain articles of diet, and it is quite possible that these articles allow the bacteria normally present in the intestines to proliferate with abnormal rapidity, or that they reduce the resistance which the flora of the intes-

tines normally exerts against foreign invaders. In some cases, however, they cause the indigestion by directly influencing the secretions poured into the intestinal canal. The first of these possibilities seems to be exemplified in the case of infants, for in them some very slight qualitative or quantitative change in the food may induce a dangerous proliferation of bacteria, quite independently of the bacterial contents of the food ingested.

The evidence would indicate that this applies also to adults.[122] A severe colitis, for example, may be caused to disappear by the giving of proteids in place of carbohydrates. In my opinion, abnormal bacterial activity occupies the foreground even in digestive disturbances produced by errors of diet.

On the other hand, the abnormal bacterial growth may follow changes in the secretory or motor functions of the intestines. The normal emptying of the fæces is one of the most important means by which abnormal bacterial growths are limited; and changes in the secretions are perhaps of equal importance.

How frequently the normal inhabitants of the intestinal tract produce disease has not yet been fully determined. It is certain that they may give rise to a peritonitis when the bowel ruptures or when its wall becomes abnormally permeable, as happens in strangulation. Local infections may take place when the intestinal wall is injured, and this is the probable cause of many cases of colon bacillus cystitis. Beyond this we know little about such enterogenous auto-infections. (Generalized infections with the colon bacillus have, however, been frequently demonstrated by blood-cultures.—Ed.) Possibly some of the infantile diarrhœas are caused by a change in virulence in the normal intestinal flora.

(The factors concerned in the causation of **infantile diarrhœas** seem to be considerably more complex than was at first supposed, and have recently received a great deal of attention. A dysentery bacillus similar in many ways to the Shiga organism has been isolated in a large number of cases.[123] In others, the colon bacillus, the bacterium lactis aerogenes and the ordinary pyogenic cocci seem to have played a prominent part, either alone or associated with the dysentery bacillus. It is possible that the bacterial rôle has been overestimated and that other conditions, such as an increased permeability of the intestinal wall, allowing an augmented absorption of toxic materials, bacterial or metabolic, are also of great moment. Such an increased absorptive tendency,

it would seem, may be caused by the intense summer heat.[124]—Ed.)

An abnormal growth of bacteria in the intestines may harm the body in several ways. Either the poisons formed may be absorbed and cause a general toxæmia, or they may act directly upon the mucosa itself and so interfere with its functions. Frequently the mucosa undergoes anatomical alterations, such as degenerations of the epithelium, inflammations and ulcerations. These latter are important, for when they occur, the barriers to invasion are let down and bacteria may penetrate the mucosa and cause a general infection.

Various toxic compounds result from bacterial decompositions in the bowel. Of these, some, such as lactic acid, butyric acid and acetic acid, have already been mentioned in speaking of the abnormal fermentative processes in the stomach. These acids are regularly produced in the small intestines; but under pathological conditions, the quantity so formed may be enormously increased. They irritate the intestines, increase the peristaltic movements and may cause lesions of the epithelium. This is particularly the case in infants because of the greater susceptibility to injury of their intestinal lining. Gases, such as hydrogen, carbon dioxide and methane, likewise may be produced in excessive quantity and cause tympanites and intestinal colic.

An excessive proteid decomposition in the intestines gives rise to all the various products of putrefaction, among them indol, skatol, phenol and other compounds belonging to the aromatic series of compounds. Many of these are rendered non-toxic after absorption, through combination with sulphuric acid, glycocoll, glycuronic acid, etc. These combinations apparently take place in the liver,[125] and the compounds thus produced are excreted by the kidneys. These aromatic bodies are normally formed almost exclusively in the large intestines. Their amount depends upon a variety of factors, of which the most important are the quantity of material in the chyme that can undergo putrefaction, the amount of substances present which will exert an antiseptic action, the varieties of bacteria present and the rapidity with which the material passes through the intestines.

(Our best index of the amount of putrefaction which is taking place in the intestines is the quantitative deter-

mination of the ethereal or aromatic sulphates in the urine;[126] for, as has been said, the aromatic products of putrefaction are largely eliminated as such sulphates, when once they have been absorbed from the intestines; while the quantity of these substances arising in the metabolic processes is negligible. An increased output of these bodies in the urine speaks particularly for intestinal stasis. Ordinary constipation is often associated with a more or less marked increase, and intestinal obstruction is regularly associated with the elimination of large quantities of ethereal sulphates in the urine.

We do not know how serious the absorption of these aromatic bodies from the intestines is. Indol, when administered by mouth, is only moderately toxic, and individuals vary considerably in their susceptibility to its action. Small doses are liable to produce frontal headaches and a condition of nervous irritability and restlessness; larger doses may cause diarrhœa, or marked irritability, insomnia and mental restlessness. The continued administration of enough indol to cause a constant and decided reaction for indican in the urine is capable of inducing neurasthenic symptoms. It is very probable, therefore, that the neurasthenia which is so often seen in cases of chronic intestinal indigestion is in part due to the absorption of the aromatic products of putrefaction.—Ed.)

It is also possible that the nephritis which so frequently follows intestinal obstruction is caused by the products of intestinal decomposition.[127]

Many disturbances in the function of the intestines have been ascribed to the action of protozoa, though their etiological relationship has been well established for only one disease—endemic dysentery.[128] The virulence of the ameba of dysentery for cats leaves us in no doubt as to its pathogenicity. Yet not all cases clinically classified as dysentery are due to the action of this amœba.

The Pathology of Absorption.—Absorption takes place throughout the small intestines, being more rapid for organic substances at least, in the upper than in the lower portion. According to the most trustworthy observations, but little nutritive material is absorbed by the large intestines.

The manner in which many diseases of the intestines affect the absorption of food is not fully known. Those circulatory

disturbances that produce a slower blood-current lead to a diminution in the absorption of fats, but do not affect that of sugars and proteids.[129] Fat absorption is also reduced whenever the lymphatic vessels that drain the intestines are obstructed, as may happen in tuberculosis of the mesenteric lymph-nodes. The diseases that affect the intestines only in isolated areas, such as typhoid fever, have almost no influence upon absorption. On the other hand, wide-spread diffuse diseases of the mucosa, such as enteritis and amyloid degeneration, as well as caseation of the mesenteric lymphatic nodes, will diminish the fat absorption if they are moderately severe, and will reduce the absorption of all kinds of food if they are very severe. This loss of material is caused partly by the changes in the mucosa itself and partly by the rapid passage of the food through the intestinal tract, though diarrhœa alone does not necessarily diminish absorption.[130] On the whole, our knowledge of this important field is extremely limited, particularly with respect to disturbances of absorption in the individual intestinal, and also systemic, disorders. In tuberculosis, without bowel involvement, Plesch[131] has found that the absorption of all types of food material is reduced by one-half.

In the healthy individual, the greater part of the water in the food is absorbed in the upper small intestines.[132] If the amount of water in the intestinal contents be increased, this may arise, first, from a diminished absorption of water from the food, due either to the presence of salts or other bodies which raise the osmotic tension of the intestinal contents, or to a too rapid passage of the chyme through the intestines. A rapid transit of material through the large intestines always diminishes the absorption of water. Drinking large amounts, on the other hand, frequently has no effect upon the fæces.

In the second place, an increase in the amount of water in the fæces may result from excessive secretion. We know that the stomach secretes water readily, and there is abundant reason to believe that the intestines may likewise furnish large quantities of fluid to their contents, either by the process of transudation or by that of secretion. The most remarkable example of watery fæces is furnished by the "rice-water" stools of Asiatic cholera. These contain only a trace of albumin, an amylolytic enzyme and hardly any salt except sodium chlorid. Their composition approaches that of the nor-

mal intestinal secretion, differing from an ordinary inflammatory exudate in the low proportion of proteids present and in the amylolytic ferment.[133] Cohnheim believed, therefore, that the rice-water stools of cholera were caused by an increase in the intestinal secretions, rather than by an inflammatory exudation. Yet later researches have shown that the essential pathological process in cholera is an intense inflammation of the mucous membrane, so that the question as to the inflammatory or secretory nature of the fluid still remains unsettled.

(The theory of MacCallum[134] that saline cathartics produce a watery stool purely by their stimulation of the intestinal secretions has not been confirmed by the more recent work of Frankl and of Auer,[135] who found that these concentrated salts act principally by virtue of their power to absorb and to hold water, and that their stimulative effect is of subordinate importance. They found further that the subcutaneous and intravenous injections of the salines do not cause diarrhœa; in concentrated solution, indeed, they may cause constipation by inducing diuresis and loss of water from the blood and tissues.—Ed.)

Disturbances in the Intestinal Movements.—In discussing this subject, it is necessary to consider separately the small and the large intestines, for the peristaltic movements in each are quite different. During a complete fast, rest prevails throughout the entire gastro-enteric tract, whereas digestion leads to peristaltic movements of the small intestines. These consist, in the first place, of progressive waves of contraction which affect the circular muscle over a limited area, and which travel forward, tending to carry the chyme with them. The second form of movement is produced by a simultaneous contraction of the circular and longitudinal fibres, and this results in a twisting of the intestinal coils, which tends to bring different parts of the chyme into contact with the mucosa. (Meltzer and Auer[136] have described a third movement of the small intestines —the so-called peristaltic rush, which consists of a rapid peristaltic contraction, following a relaxation of a considerable part of the small bowel—which may even pass uninterruptedly from the duodenum to the ileocæcal valve. Rhythmic segmentation (Cannon) is another type of movement observed in the small intestines. In cats fed with food containing

bismuth, the Röntgen rays show a rhythmic breaking up of the food column into small segments, which are then joined together again. The process occurs at the rate of thirty times a minute in the cat. This movement serves to mix the contents of the bowel and not to further their progress, which depends rather upon an associated peristalsis. Antiperistalsis, finally, may be observed in cases of obstruction in the small bowel.—Ed.)

According to Holzknecht,[137] the colon of the healthy individual exhibits rhythmic propulsive waves, which impel the fæces onward for a considerable distance and then cease for several seconds. Three or four such waves serve to drive the fæcal column through the entire large bowel. Other observers, however, deny the existence of this peristaltic movement. It would appear, furthermore, that a kind of contraction ring is situated half-way along the transverse colon, at which point the formation of the stool begins. Proximal to this ring, the chyme remains relatively motionless; when it tends to move forward, it is forced back into the cæcum by antiperistaltic waves. By this means the contents of the large bowel are thoroughly mixed and absorption is not hurried.

Zülzer[138] has described substances which arise in the stomach wall during the process of digestion, and which, if injected into rabbits, cause a lively peristalsis extending throughout the intestinal tract. This same body—called by him "peristaltic hormone"—occurs also in other organs, particularly in the spleen. The physiological significance of this hormone in the initiation of intestinal peristalsis is not known; practically, however, it has proved of value in the treatment of certain cases of constipation.

Diarrhœa.—Defecation is a partly voluntary, partly reflex act, which is initiated by the presence of more or less fæces in the rectum. In many individuals defecation occurs regularly at the same time each day, while in others it occurs very irregularly. In diarrhœa, the large intestines fill rapidly and frequently with fluid contents, and their peristaltic movements are increased. Added to this is an inhibition of the antiperistaltic waves already referred to, which normally tend to hold the fæces back until properly constituted. The small intestines, however, may or may not be affected. The milder and more transitory diarrhœas usually do not involve the small intestines, as may be inferred from the

character of the fæces. On the other hand, in many conditions, such as typhoid fever, the small intestines are affected and the stools contain undecomposed biliary pigments and abnormal quantities of unabsorbed food material. This difference in the behavior of the large and small bowel is not well understood. It is possible that a given stimulus produces a lively peristalsis in the one and has little or no effect upon the other.

Nervous Diarrhœas.—The cause of the diarrhœa may lie outside of the intestines. In many individuals a mere cooling of the skin or a feeling of nervousness will produce diarrhœa without necessarily disturbing the general health. A gradual transition may be seen in such cases from the physiological to the pathological; in the one, a pronounced stimulus is necessary to produce any effect, whereas, in the other, a little excitement or even the fear of a diarrhœa may be enough to bring it on. Such individuals often show other neurasthenic or hysterical stigmata. It seems probable that their central nervous system affects the peristalsis of the intestines through the vagus and splanchnic nerves. Even normally, the peristaltic movements are influenced to a certain extent by the central nervous system, while in these pathological conditions this influence is greatly exaggerated. In some of these cases, however, the irritability of the intestines themselves may possibly be increased so that they respond excessively to normal stimuli.

Diarrhœas may also accompany anatomical diseases of the nervous system, as happens, for example, in the intestinal crises of tabes. It is quite certain that in these cases the diarrhœas are dependent upon changes either in the nerves or in the central nervous system, yet definite proof of this is wanting. The watery character of the fæces in nervous diarrhœas may be due, in part, to the rapid transit of material through the intestines, though it seems probable that it is more often caused by a nervous hypersecretion from the intestinal mucosa, a condition which would find an analogy in the well-known instances of nervous secretion of saliva, gastric juice and urine.

In hysterical girls, the small intestines are frequently the seat of increased peristalsis, often giving rise to constant gurgling sounds, without, however, causing diarrhœa. That these peristaltic movements are dependent upon mental influences is sup-

ported by the fact that they are most liable to occur at the very times at which the patient wishes to suppress them.

When the hypersecretion affects the large intestines, the mucus and proteids in the secretion may form tubular and membranous casts, which are afterwards passed in the fæces. This disease, known as colica mucosa (membranous colitis), has, in most instances at least, nothing whatever to do with an inflammation of the mucous membrane,[139] but is a pure secretory neurosis. It usually occurs in nervous women, and may be accompanied by the most violent paroxysms of colic. At times, however, very similar membranous structures may result from true inflammatory processes in the intestines, for example, in convalescence from typhoid fever.

Diarrhœas in General Diseases.—Intermediate between these diarrhœas of nervous origin and those due to causes situated within the intestines, is a second group, *viz.*, those that accompany general diseases. Several possibilities suggest themselves as to the cause of this class of diarrhœas. In the first place, the general disease may so weaken the resistance of the intestinal mucosa that the latter falls a prey to the normal flora of the intestines or to bacteria which are introduced into the gastro-intestinal canal, either by mouth, or by the secretions from the infected body. In the second place, toxins produced by the general disease may directly cause the diarrhœa, just as do other poisons. Some infectious diseases, such as pneumonia, rarely cause diarrhœa; whereas others, such as measles, frequently do so. Diarrhœa not infrequently complicates chronic nephritis.

Diarrhœas of Intestinal Origin.—The third and most important class of diarrhœas is that caused by the excessive stimulation of the intestinal mucosa by the intestinal contents. The materials which act as stimulants are in the first place coarse, hard food remnants, especially cellulose, which resist the action of the intestinal secretions and bacteria. In the second place, and more commonly, the peristalsis is excited by chemical irritants, which may either be introduced from without or be produced within the intestinal canal. Of these, we shall name only the organic acids and the gases which result from fermentation.[140] These are of the greatest importance in the production of many diarrhœas. Whether or not water alone will increase the peristalsis has not been definitely settled. We know,

however, that diseases which interfere with the absorption of water by the small intestines may lead to diarrhœa, as is the case with amyloid degeneration of the intestines.

Diarrhœa is favored by an increased irritability of the intestinal mucous membrane, muscle or nerves, for normal stimuli then give rise to excessive responses. Such an increased irritability of the intestines is probably present in most acute inflammations of the mucous membrane. In acute enteritis, for example, the diarrhœa is due to the combination of two causes —increased intestinal irritability and increased stimulation of the intestines by the products of abnormal fermentations. In chronic enteritis there is frequently no increase in the irritability of the mucous membrane. Even in intestinal ulcerations, the irritability may not be increased, this being especially true of the chronic ulcerations.

The effect of diarrhœa upon the body depends to a great extent upon its cause. If the food is hurried through the upper part of the small intestines, its absorption may be seriously interfered with and the patient may suffer from malnutrition. On the other hand, when the diarrhœa is due entirely to an increased peristalsis of the large intestines, it is often surprisingly well borne, for the most nourishing part of the food has already been absorbed before the large bowel was reached.

Constipation.—In constipation, the chyme remains in the large intestines for an abnormally long time, and more water is absorbed from it than usual, with the result that the fæces become hard and are passed less frequently than usual.[141] It is impossible to draw any sharp line here between what is pathological and what is physiological. We may say in general, however, that infrequent defecation can only be regarded as pathological when it gives rise to symptoms. Constipation is undoubtedly caused by abnormalities of the large intestines; yet it is unprofitable to speculate on the exact nature of these abnormalities so long as we do not even know why the normal intestines empty themselves so infrequently.

Causes of Constipation.—In a certain proportion of cases the constipation is caused by improper food. We have stated that the material in the bowels furnishes the normal stimulus to intestinal peristalsis. Every animal must take food that furnishes the necessary amount of stimulus. Thus an herbivore will die of constipation if it be totally deprived of the cellulose which nor-

mally excites its peristalsis, and even carnivorous animals may suffer seriously from constipation if fed solely on such easily absorbable material as milk, eggs and meat. A certain number of men place themselves on just such a diet. Though their intestines possess a normal irritability, the stimulus to peristalsis is lacking and they suffer from constipation. If they take foods which stimulate the intestines either by reason of their coarse, indigestible character, or because of their content of chemical irritants, such as the organic acids, then the constipation is cured. A lack of water in the chyme may also lead to constipation. This is probably the cause of the form which so frequently accompanies dilatation of the stomach, with hypersecretion and the vomiting of large quantities of fluid.

In other cases of constipation, the normal irritability of the intestines is reduced more or less, and consequently the normal stimuli are not followed by the customary response. This is apparently the cause of the constipation which sometimes accompanies chronic catarrh and atrophy of the mucous membrane of the large intestines.

It is evident that no irritation will prove of any value when the muscular coat of the intestines is greatly weakened by muscular paralysis or atrophy.[142] Such a muscular atrophy may or may not be associated with atrophy of the mucous membrane. Peritonitis is frequently accompanied by constipation and even by total paralysis of the intestines.

Although the ganglia and their nervous connections within the intestinal walls are now believed to control peristalsis,[143] nevertheless the exact effect of disease of these structures is not known. Degeneration of this nervous apparatus has been described in cases of lead poisoning and of chronic constipation, yet similar changes have been observed in other conditions.

Constipation may be associated with diseases of the central nervous system, such as neurasthenia, melancholia and many organic changes. The cause of this constipation is not always clear. The view that it is due to a spastic condition of the muscle of the large bowel is scarcely tenable, not only because tonic contractions of smooth muscle can scarcely persist for months and even years, but also because the clinical picture is quite different from that of spastic constipation.

Thus we see that many causes may lead to constipation. Improper food, reduced irritability of the intestines, weakness of the intestinal musculature, abnormal nervous influences—all may act independently or in combination. Some cases of constipation are cured by exercise, although we do not know how it is effected.

The act of defecation is often assisted by the contractions of the abdominal muscles, although in the perfectly healthy man this is not necessary, and the peristalsis of the large intestines suffices to empty them. In most cases of constipation, the intestinal peristalsis is primarily at fault and it is rare to find the rectum filled with unexpelled fæces. If such be the case, however, then either the presence of the fæces in this locality fails to produce the normal stimulus to defecation, or the abdominal muscles do not furnish the help which may be necessary to expel the accumulated material.

Finally, there is a form of constipation which is due to a tonic spasm of the smooth muscle of the intestine.[144] Such a spasm may be produced by the action of lead and by meningitis; and the condition may also occur in association with neurasthenia and hypochondriacal conditions. In spastic constipation, certain portions of the intestines, especially of the colon, are firmly contracted and do not propel the chyme. Antiperistalsis is possibly an additional factor.[145] These contracted intestines may sometimes be felt through the abdominal wall as round, hard, somewhat sensitive cords. The spasm of the intestines frequently causes colic, and the fæces are often hard and of small calibre, the latter the result of the spasm.

Effects of Constipation.—The effects of constipation are for the most part subjective, and the general nutrition of the patient rarely suffers. Defecation is often extremely difficult, and the worry about this tends to upset the nervous equilibrium of the patient. Immediately after defecation he feels brighter and his head feels freer. These sensations are partly suggestive, as is evidenced by the fact that they are most pronounced in individuals who worry most about their condition.

Yet they are not entirely suggestive, for leaving out of consideration the ill-defined and much-abused application of the term auto-intoxication, we meet with cases of constipation exhibiting albumin and casts in the urine, both of which disappear after a thorough evacuation of the bowels.[146] And the same

urinary anomalies may appear in cases of constipation produced by opium or tannalbin. We must not lose sight, therefore, of the possibility of the absorption of toxic materials.

Intestinal Obstruction.—Two degrees of intestinal obstruction are recognized—the incomplete and the complete. Among the factors leading to delay or complete blocking of the progress of the intestinal contents are inflammatory and malignant strictures, foreign bodies, gall-stones, invagination, kinks in the bowel, compression from without and strangulation in hernial openings and by fibrous bands. The view that paralysis of a short portion of the bowel may be equivalent to a stenosis is no longer tenable; for the chyme suffers no delay in passing through a section of intestine made inactive by a sarcomatous infiltration of its walls. When stenosis does occur in a paralyzed loop, it is due to a kinking in the latter, the result in turn of its lack of tone and of the torsion which it undergoes in its overfilled state. This is a frequent mechanism in postoperative ileus.

Pockets—either congenital or formed by inflammatory bands—are of common occurrence in the peritoneal cavity; among such are the bursa omentalis and those formed by inflammatory adhesions about the cæcum and in the pelvis. Into these openings slips a loop of bowel, not as a result of peristaltic movements, but by virtue of the combined action of gravity and the contractions of the abdominal muscles. Here the loop may be merely fixed, or incarcerated by the elastic recoil of the distended hernial ring. In external hernias this mechanism is especially well illustrated. In consequence of the constriction, there occurs a rapid venous stasis in the affected loop of the bowel, followed by œdema, an increase in volume of the loop, and finally, when the hernial ring can no longer accommodate the swollen bowel, an obstruction to the fæcal movement.

In cases in which the stasis and œdema are less marked and the portion of intestines is firmly fixed but not incarcerated, the loop may increase in size by another mechanism, as pointed out by Wilms.[147] Here, peristalsis impels the contents of the herniated bowel toward the hernial opening, where a further movement is hindered by the greater or less obstruction existing at the ring. As a result, the impeded contents distend the bowel at this point, the distention serving to pull upon the gut behind it. To

this pulling is added the tensile force of the rapidly accumulating contents, as incarceration proceeds at the hernial ring.

No adequate explanation has yet been given for the sudden obstruction that sometimes develops in hernias which have existed for a long time without producing symptoms. Experiments on the cadaver have, indeed, demonstrated that when the intestinal coils are overfilled it is difficult to empty them, for they tend to become kinked, and the mucous membrane often slides over the muscularis, so that it lies in folds at the neck of the sac. Yet these experiments do not explain why, at a particular time, the intestines should become overfilled; and, furthermore, the neck of the sac may not be especially narrow in these chronic cases. It seems to me that insufficient attention has been paid to the possibility that there may be a primary paralysis of the muscularis in these cases, which would allow the intestinal contents to accumulate at one spot. This hypothesis may possibly serve to explain many cases in which no mechanical cause can be found for the obstruction. The question cannot be finally answered, however, until we possess more evidence from clinical and experimental sources.

If a piece of intestine possesses a long mesentery with a short attachment to the posterior abdominal wall, as is the case, for example, with the sigmoid flexure, it is liable to become twisted about its pedicle, thus producing the condition known as volvulus. The rapid distention with gas that follows the volvulus interferes with the movements of the intestines and prevents them from untwisting, and the lumen of the canal is obliterated at the point of twisting.

Intestinal obstruction may result finally if a portion of the intestines is carried downward toward the anus within the portion immediately succeeding it. The cause of such an intussusception is somewhat obscure.[148] It cannot be reproduced experimentally by the mere paralysis of an intestinal loop. It would appear rather as if one portion of intestines drew itself over another that was tetanically contracted, and that the invagination increased by the successive inclusion of freshly contracted portions. A similar process is frequently seen in the normal intestines, but the invagination is then neither extensive nor permanent. We do not know what interferes with a straightening out of the canal in the pathological cases. When the invagination

has once passed beyond a certain limit, the circulation of the enclosed intestines is interfered with, and œdema follows.

In all these obstructions the symptoms depend mainly upon the degree of stenosis and the rapidity with which it develops. If the lumen of the bowel is only partially and gradually encroached upon, the intestines lying immediately above the obstruction contract more forcibly than usual and their muscular tissue undergoes hypertrophy.[149] The cause of these increased contractions resides essentially in the greater work demanded of the hypertrophied muscles. A moderate stenosis may last for months without giving rise to any symptoms other than slight constipation whenever the food is not properly chosen. When the hypertrophy can no longer keep pace with the amount of work demanded, the manifestations of stenosis appear. This occurs sooner in the large than in the small bowel, as is most clearly seen in old age.

If the lumen of the bowel is totally occluded, the resulting symptoms are entirely different from those of a gradual and partial obstruction. A total occlusion may develop acutely, or it may come on during the course of a chronic obstruction, owing to the inability of the muscle to force material past the partial stenosis. In either case the intestinal contents stagnate above the point of obstruction. The bacteria then multiply rapidly, for their growth is no longer held in check by the onward movement of the chyme. The resulting decompositions are of various kinds, depending partly upon the bacteria present and partly upon the material subjected to their action. When the obstruction affects the lower part of the small intestines, large quantities of unabsorbed food material stagnate, and putrefaction is very marked; whereas, if the large intestines are affected, some time may pass before any abnormal decomposition is apparent, because most of the nourishment has already been extracted from the chyme. When putrefaction occurs, all its varied products are formed, and often in large amounts. Of these, the aromatic compounds, such as indol and phenol, combine in the body with sulphuric acid to form the comparatively harmless ethereal sulphates. As a result there is often a marked increase in the quantity of indican and of ethereal sulphates in the urine (see p. 281). It is possible, however, that some of the poisonous compounds resulting from the intestinal decomposition may escape

neutralization, and that they are responsible for many of the general symptoms of intestinal obstruction. For example, the complicating nephritis is possibly of such a toxic origin.

The most frequent symptom of intestinal obstruction is obstinate constipation. Yet in certain forms of obstruction, especially in intussusception, there may be diarrhœal discharges, composed not of fæces, but of inflammatory or secretory products of the mucous membrane at and below the obstruction.

As a rule, however, the portion of the intestines below the obstruction is totally paralyzed, and not even flatus escapes through the anus. Gases collect above the obstruction and gradually back up in the direction of the stomach. The intestines which are thus distended contract vigorously, peristaltic and tetanic contractions alternating with each other. These can be frequently observed through the abdominal wall, especially if the obstruction is an old one and the muscularis has had time to hypertrophy. These muscular contractions, especially the tonic ones, frequently give rise to the most violent colic. The patient begins to vomit soon after the obstruction sets in. At first, the vomitus consists merely of the gastric contents mixed with bile-stained material from the duodenum. If the vomiting continues, however, thin, greenish-yellow material, of a fæcal odor, may appear.[150] This material undoubtedly comes from the intestines, and is composed in part of unabsorbed, decomposed food, and in part of the products of intestinal secretion.

The mechanism by which this material reaches the stomach is not perfectly clear. One's first thought would be that antiperistaltic movements play an important part,[151] for these occur in other conditions, and, even though they have not been directly observed in intestinal obstruction, no reason exists *a priori* why they should not be present. Indeed, since we have learned that antiperistalsis is normal in the colon, we are more than ever inclined to assume that a similar mechanism is present in the small intestines. (And, indeed, fluoroscopy has made us familiar with antiperistaltic waves in cases of stenosis in the small bowel and at the pylorus.—Ed.)

As the obstruction continues, the patient loses in weight and strength rapidly. The period of increased peristalsis is later followed by one of paralysis of the intestines. At first, this cessation

of intestinal movements is caused merely by the overdistention of the intestines; for it has been shown, experimentally, that greatly distended intestines cease to contract, but that they will begin to do so again as soon as the tension is diminished. In the later stages of obstruction, however, the intestinal paralysis is absolute; and, experimentally at least, no movements can be elicited. This entire absence of peristaltic movements in intestinal obstruction indicates an exceedingly grave condition, and if help is not forthcoming, the patient dies in collapse.

Though it is generally agreed that a period of increased peristalsis always precedes the period of paralysis in chronic obstruction, some consider that this primary period may be absent in acute obstruction. Yet it seems to me that a primary period of increased peristalsis is present even in these patients. When this is of short duration or apparently altogether absent, the cessation of intestinal movements is, in my opinion, usually due to an inflammation of the intestinal wall.

Strangulation.—The severity of the symptoms varies greatly in different cases of obstruction. In some, the meteorism, fæcal vomiting and collapse do not occur for days; whereas in others these symptoms develop within a few hours after the obstruction takes place. These variations depend largely upon the nature of the occlusion. A simple closure of the lumen of the intestines is much less dangerous than a so-called strangulation, which may accompany any of the different forms of intestinal obstruction.[152] In this latter condition the blood-supply of the intestines is affected. The mesenteric and intestinal veins are pressed upon and occluded, the arteries continue to send blood into the intestines, and œdema results. These vascular changes, together with injuries to the nerves of the peritoneum, are apparently responsible for the rapid and alarming symptoms which ensue. The walls of the intestines become infiltrated with fluid, and bacterial decomposition proceeds with excessive rapidity within the lumen of the strangulated bowel. The products of this bacterial activity injure the intestinal walls, so that they no longer oppose the normal resistance to the gases which are formed. Consequently the strangulated piece of intestine becomes enormously distended (local meteorism). The violent peristaltic movements produce the most intense pain, and vomiting becomes uncontrollable. Added to these are certain systemic manifestations, such as the general circulatory changes,

the collapse and the rapid loss of strength. The circulatory disturbances are caused, in the first place, by reflexes from the peritoneum that act upon the heart and vessels, but especially by those that influence the splanchnic vascular area. In the second place, they are probably produced directly by the toxic action of putrefactive products absorbed from the intestines.

Meteorism.—The intestines of healthy individuals contain gases [153] composed in part of swallowed air and in part of those which arise from the decomposition of the intestinal contents by the digestive juices, and especially by bacteria. When air is swallowed, the oxygen in it is rapidly absorbed, so that the small intestines rarely contain this gas. The nitrogen, however, remains in the canal for a much longer time. Carbon dioxide is set free by the action of acids upon the carbonates in pancreatic juice, bile and succus entericus, but it is generated in much larger quantities during carbohydrate fermentation. The latter also yields hydrogen and marsh gas; and the putrefaction of proteids produces small quantities of hydrogen sulphid. Of these various gases, the carbon dioxide is readily absorbed by the blood, the nitrogen, methane and hydrogen, on the contrary, much more slowly. The quantity and quality of the intestinal gases vary greatly, even in a healthy man; for they depend largely upon the quality and quantity of the food taken and upon the varieties of bacteria that happen to be present.

These intestinal gases may produce some variation in the size of the abdomen, but rarely does great distention result, for the normal intestines can, to a certain extent, dispose of the gases they contain, either by absorption, or by expulsion through the anus, both processes depending largely upon the tonus of the smooth muscle.

In gastro-intestinal diseases much larger quantities of gas may be formed, and those produced in greatest abundance are usually the very ones which are least easily absorbed, *viz.*, methane and hydrogen. Yet a mere increased production of gas does not necessarily cause meteorism either in a healthy individual, or even in some patients with intestinal obstruction. It would appear that a diminished muscular tonus and an insufficient absorptive capacity are of much greater importance in the production of tympanites than is an excessive formation of gases. For this reason, meteorism is especially marked in peritonitis and acute

strangulation. If the intestines once yield to the pressure of gas within them, a vicious circle is established, for this very distention embarrasses their circulation, and so diminishes their ability to absorb gas.

Meteorism tends to develop, therefore, whenever a weakness of the intestinal musculature is associated with an over-production of gas within the intestines. The milder forms of tympanites are seen in connection with dyspepsias, enteritides and typhoid fever; the more severe in association with peritonitis and intestinal obstruction.

The meteorism that is present at times in hysterical patients has not been satisfactorily explained, but seems to depend in part upon transitory paralyses of the muscle, and in part upon the swallowing of large amounts of air. Hysterical paralyses are common enough in other parts of the body, and we see no reason why they should not occur in the intestines; and the fact seems well established that many hysterical individuals swallow air in considerable quantities. That some cases may be due to a spasm of the diaphragm associated with a relaxed abdominal wall is evidenced by the fact that they disappear under anæsthesia.

Abnormal Intestinal Sensations.—These are various. In the first place, a distention of the intestines will produce the sensation of fulness in the abdomen, and if the distention be marked, dyspnœa may result, owing to the high position of the diaphragm.

Colic results from violent contractions of the intestines. It has been said that colic is never produced by the normal peristaltic movements, but only by tetanic states of the intestinal musculature. These are liable to occur whenever the stimuli for peristaltic movements are especially strong. The most severe forms of colic are seen in connection with intestinal obstruction and lead poisoning. Less severe is the colic which may accompany intestinal catarrah and cholera nostra. The pain of colic has been located by some in the muscles, in which case it would be analogous to that caused by cramps in voluntary muscles. By others, it has been located in the peritoneum, for we know that, like the other serous membranes, the peritoneum is an exceedingly

sensitive structure, and inflammations in it are always accompanied by severe pain.

The cause of painful sensations referred to the viscera is still unsettled. It has long been known that the brain is insensitive to pressure and to mechanical irritation, and a similar absence of painful sensations is true also in the case of the stomach and intestines. Lennander[154] has attributed the pain of intestinal colic to the pressure exerted by the dilated bowel upon the sensitive parietal peritoneum; while Wilms[155] regards the traction upon the sensory nerve-containing mesentery as the explanation. Both are agreed that the pain arises outside of the stomach and bowel; yet, under certain conditions, the latter may at times be the seat of pain.[156] At any rate, the idea that local anæsthesia in intestinal operations is equivalent to general, must be relinquished in view of the fact that the bowel is insensitive even when no anæsthetic is employed. Nevertheless, I am not convinced that pain may not arise in the internal organs. Possibly, the sensitiveness of an organ is more important than the strength of the irritation; or in other words, that pain originates in the viscera only when the threshold of sensibility is lowered by disease.

The pain of appendicitis and of cholecystitis is due to the inflammation present. In renal and biliary colic, the likeliest explanation of the pain is the pull exerted by a distended renal pelvis and gall-bladder, respectively, upon the nerves in the biliary passages and ureter; it is possible, however, that the most important factor is the dragging upon the peritoneum, as suggested by Wilms.

Still other pains are unquestionably to be referred to the peritoneum, such, for example, as those which accompany peritoneal adhesions. These adhesions which, as a rule, follow some previous inflammation, often cause the most annoying pain, which becomes worse when the bands are dragged upon.[157] The pain of peritoneal adhesions is of the greatest practical importance, for it may harass the patient for years after the original disease has subsided.

A somewhat similar pain is often experienced by nervous individuals, and seems to be of a neuralgic nature, for no anatomical basis can be discovered for it. It will be discussed, therefore, in connection with diseases of the nervous system.

Diseases of the anal orifice are often the source of severe pain. Each time that hard fæces pass over the inflamed or ulcerated mucosa the most intense agony is experienced. Perhaps even more unpleasant is the condition known as tenesmus, in which a constant, violent desire to defecate harasses the patient. This is especially liable to be present in diseases of the rectum. The inflammatory changes of dysentery frequently cause this constant desire to defecate, but, owing to the lack of fæcal material in the rectum, nothing is passed except inflammatory products and these with most excruciating pain.

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CHAPTER VI

NUTRITION AND METABOLISM

The activities of the living cells are associated with chemical changes within them, and with an interchange of food and waste material with their surroundings. The sum of all these processes is termed metabolism. A discussion of nutrition and metabolism ought properly to deal with each organ individually, for it is obvious that different tissues require different food materials and give rise to different waste products. Indeed, the various organs are more or less interdependent upon one another, and one organ, for example, may need material that has been elaborated by another, or may transform waste products derived from another. This interdependence—or chemical correlation,[1] as it is known to-day—predicates the activities of hormones, or substances which, elaborated by one organ, exert a specific influence upon another. Though the existence of such substances has long been assumed, it is only recently that we have acquired some knowledge of their origin and characteristics. They are the products particularly of the ductless glands, though it is probable that every organ takes a part in their formation. The disorders of these internal secretions—and our acquaintance with these disorders is still largely undeveloped—we shall consider in connection with the various processes in which they play a rôle.

In the present state of our knowledge, however, we are unable to discuss metabolism from the standpoint of the individual organs, but are obliged rather to consider the metabolic processes that take place in the body as a whole. Our knowledge of these processes is derived mainly from examinations of the food ingested and of the various waste products eliminated.

The Quantitative Variations in the Metabolism of Proteids and Fats

In order to maintain the body, it is necessary to supply it with water, mineral salts and organic bodies, *i.e.*, proteids, carbohydrates and fats. It is not quite certain, however, that this enumer-

ation is complete and that there are not other, still undiscovered, needs of the body.

The Caloric Needs of the Body.—The food ingested is utilized partly to repair the tissue waste, and partly to furnish energy for muscular movements, bodily heat and for the respiratory and circulatory activities. For these last purposes, it is practically immaterial in what form the energy is provided—whether it be as carbohydrates, fats or proteids—the essential point being that the quantity of food is sufficient. The energy contained in the various foodstuffs is transformed by the body into mechanical work, chemical work and especially into heat. Indeed, Rubner[2] has shown that almost the entire energy of the food leaves the resting body in the form of heat, and that the heat which results from combustion in the body is the same as that which would be produced were the foods burned outside to the same waste products.

(The unit for measuring quantities of heat is the large calorie, which represents the amount of heat necessary to raise the temperature of a kilogram of water one centigrade degree. When equal weights of different foodstuffs are burned in the body, different quantities of heat are liberated. Thus each gram of fat produces about 9.3 calories, each gram of carbohydrates about 4.1 calories, and each gram of proteids about 4.1 calories. It will be seen from these figures that the energy derived from fat is relatively greater than that derived from carbohydrates or proteids. Indeed, one gram of fat furnishes about the same energy as do 2.3 grams of either of the other two. It is possible, with certain limitations, to replace any constituent of the diet by any other, without disturbing the equilibrium of metabolism, providing due attention be paid the caloric value of each foodstuff. Each gram of fat in the food, for example, may be replaced by 2.3 grams of carbohydrates, etc. It is furthermore possible to calculate the total quantity of energy contained in any particular diet and in this manner to estimate whether or not this diet contains a sufficient amount of energy to cover the caloric needs of the individual.

The amount of energy that must be supplied to the body depends primarily upon the activities of the tissues, and is subject to many influences. This amount has been estimated empirically from the mean quantity of food taken by different individuals.

We quote from Lusk[3] the following "standard" dietaries for a man of seventy kilograms:

(Weights in Grams)

	Voit	Rubner	Atwater
Light Work:			
Protein	....	123	100
Fat	....	46	*
Carbohydrates	....	377	*
Calories	....	2445	2700
Medium Work:			
Protein	118	127	125
Fat	56	52	*
Carbohydrates	500	509	*
Calories	3055	2868	3400
Hard Work:			
Protein	145	165	150
Fat	100	70	*
Carbohydrates	500	565	*
Calories	3574	3362	4150

* Carbohydrates and fats to make up the full value.—Ed.)

A small person needs a relatively greater supply of energy per kilo of weight, for, as is well known, a small body has a relatively large surface, and consequently loses more heat in comparison to its weight. This is one reason why children need more food than adults in proportion to their weight. On the other hand, stout individuals need relatively less food; instead of the normal thirty-four to forty-five calories, they require only about twenty-six to thirty-six calories per kilo of body weight. This difference is due to the fact that a large body has a relatively small surface; that the thick layer of fat protects these persons from heat losses; that the fat itself is practically dead tissue in the body and does not consume energy; and, finally, that stout individuals usually take a minimal amount of exercise.

Not all variations in the caloric needs of different individuals are thus easily explained, and there are reasons for assuming that the cells of different persons manifest different needs for energy. At least, no other satisfactory explanation can be given for the fact that certain men seem to require very much smaller quantities of proteids and of energy than do others.

The Proteid Needs of the Body.—The food must furnish the body not only with a sufficient amount of energy, but also with a certain minimum of proteids, which is utilized in part in the

repair of the waste within the cells. In view of the extensive splitting undergone by the proteids in the intestines,[4] it is conceivable that the body might be properly maintained if, instead of the proteids themselves, their split-products (amino-acids and ammonium salts) were substituted in correct proportion. And, in fact, this has been done with success, using the products of the digestion of meat and milk. Unpublished studies of Grafe would indicate that in young undernourished animals whose diet has contained insufficient proteids and an excess of carbohydrates, ammonium salts are indeed utilized, if one may judge from the persistently high percentage of ammonia nitrogen retained.

The minimal amount of proteid[5] necessary for the needs of the body varies with the condition of proteid nutrition that is to be maintained, with the kind of proteid given, with the nature and amount of other foods given and with the work which the body performs. The lowest minimum recorded[6] is 0.02 gram nitrogen per kilogram body-weight. Although the quantity given by Voit seems considerable (one hundred and eighteen grams of proteid for a man of seventy kilograms), and although less (even twenty-five to forty grams) is sufficient for an individual when other forms of food are taken in great abundance,[7] nevertheless there is a growing inclination to regard these older figures as approximately correct for a healthy individual, and to believe that the capabilities of the body are apt to be diminished if less than this amount of proteid food be taken. On the other hand, as Rubner has shown, proteids in the food should not exceed a certain maximum proportion, for if they do, an excessive amount of heat is liberated immediately after meals, and this is not only useless, but may be directly harmful if the heat regulation in the body be imperfect.

The cells are capable of repairing their proteid waste irrespective of whether the food contains a diversity of proteids or a single one. But in what way the proteids are conveyed to the cells is not known, though it is likely that the source is the blood plasma. Nor is it known whether the cells are supplied with fully formed proteids or with the split-products of the latter from which they synthetize their own proteids.[8] That the body may build up its nucleins for the most part is known.[9]

Certain facts lead us to believe that even the minimal proteid requirement is considerably in excess of that needed to repair

tissue waste. This excess enters into the formation of energy. In this second function, however, proteids may be entirely replaced by carbohydrates and almost completely by fats.[10]

Inanition.—Inanition may be due to a variety of causes. Of these the most important are, first, an insufficient ingestion of food—either from lack of food or lack of appetite—and secondly, an insufficient absorption of material from the gastro-intestinal canal. Practically, inanition is most frequently seen in connection with diseases of the digestive system.

It is necessary to distinguish an insufficient supply of food as a whole—a caloric insufficiency—from an insufficient supply of proteid material—a proteid insufficiency. These two are more or less independent of each other, it being possible, for example, that a patient should gain in weight, and yet suffer from an insufficiency of proteids, or *vice versa*.

If too little food be supplied to the body, the individual must live upon his own tissues. His glycogen and fats can furnish him with energy. In addition to this, however, he consumes a certain minimal quantity of proteids, which is, for the most part, sacrificed by the less important organs of his body. The amount of proteids thus consumed depends partly upon the quantity of fat and glycogen at his disposal and partly upon individual peculiarities, which, in a particular case, tend to maintain it at a fairly constant level. During the first few days of an absolute fast the excretion of nitrogen is comparatively high, owing to proteids that had been taken just before the fast began. As this excess of nitrogen is being eliminated, the quantity in the urine gradually sinks to a minimum; though the fall is sometimes interrupted about the third or fourth day, possibly because the glycogen in the body is exhausted. Toward the end of the fast the premortal rise of nitrogen excretion occurs, which is due to the lessened amount of fat for consumption and to a larger derivation of energy from the proteids alone.

During the earlier stages of starvation, therefore, the energy necessary for muscular movements and for heat is supplied by the combustion of the glycogen and fats stored up in the body. The more valuable proteid material is thus protected from con-

sumption. When the store of non-nitrogenous material comes to an end, however, the proteids themselves must be utilized to supply the necessary energy to the body.[11] The living tissues then break down rapidly; yet a certain discrimination still takes place. The more important organs live at the expense of the less important; and Voit has shown that the former will retain their normal weight practically unaltered to the end. The greatest loss is sustained by the muscles, glands and fatty tissues; while the heart and central nervous system are spared to the very last.[12]

Absolute starvation is rarely seen by the physician, but partial inanition is by no means infrequent, and its treatment furnishes one of the most important problems that confront him. Usually, in these cases, both the total caloric energy and the proteids in the diet are insufficient. The amount of this deficiency may vary up to absolute starvation.

The effects of starvation upon the individual depend, in the first place, upon how complete it is. If the body consumes thirty-five calories per kilo a day, and receives only ten from the food, it must supply twenty-five calories from its own substance, and the condition is naturally a much more serious one than if it had received thirty calories in the food and had supplied only five from its own substance. Furthermore, starvation is withstood much better if the patient be stout, for he then has a larger amount of fat that can be utilized to supply energy. This serves to postpone the time at which the non-nitrogenous stores in the body give out, and the living tissue itself must be consumed to supply energy. Finally, the course of inanition is influenced by the demands made upon the energy within the body; thus, the condition is a more serious one when the individual must work, or when he is not well protected by clothing, etc., from losses of heat.

In certain diseases, hunger and insufficient nourishment are often surprisingly well borne —better indeed than they are in health—for the body seems to be able to limit its consumption of proteids and energy. Astonishingly low figures have been found in such cases; indeed, patients have often gained in weight on a diet that would be entirely insufficient for a healthy man.[13] The amount of heat produced in the body during a short fast is about the same as when the individual is consuming moderate amounts of food. If

the patient suffers from prolonged partial starvation, however, the amount of heat produced in the body seems to be lessened; and it would seem that the ability to limit the expenditure of energy is much greater in wasting diseases, such as diabetes, for example, than in hunger states of short duration in which no opportunity is given for accommodation to the new conditions.

The Effects of an Oversupply of Food.—It is necessary to discuss the effects of increasing the nitrogenous and the non-nitrogenous elements in the food separately, for the laws governing each are different. We may say, in a general sort of way, that the cells of the body ordinarily decompose all the proteids taken in the food. When proteids are taken in abundance, and the total caloric energy of the food is not too greatly increased, there is merely a slight retention of nitrogenous material during the first few days of the new diet. Very soon, however, the body reaches a condition in which it is consuming all the proteids furnished to it, and it is then said to be in nitrogenous equilibrium.

If the tissues happen to be in need of new material, as is the case during growth and convalescence, it is possible that a considerable proportion of the extra supply of proteids may be retained in the body and may be built up into living tissue.

It is even possible to cause a considerable retention of nitrogenous material in the bodies of normal animals by feeding them with large quantities of both nitrogenous and non-nitrogenous food.[14] Apparently the same result may be attained even more easily in man.[15] We do not know certainly whether this nitrogenous material is retained in the body as proteids or as other compounds. It is interesting to note in this connection that when growing children or convalescents retain nitrogenous material in their bodies, they are taking a diet that contains an excessive amount of energy.[16]

The ingestion of fats, but especially of carbohydrates, in great excess tends to diminish the excretion of nitrogen in the urine; or, in other words, it tends to cause a retention of nitrogenous material in the body. This fact has been variously interpreted. E. Voit considers that the cells utilize those foods which are supplied to them in greatest abundance; whereas Pflüger and others believe that the selection of material for consumption is a property of the living protoplasm,

and as such is almost independent of which foods are supplied in excess. We cannot enter into a discussion of this physiological problem, but may state our belief that the growth of living tissue depends primarily upon the activities of the cells. In virtue of some unknown property, the cells grow and multiply, and their growth and multiplication are especially excited by functional activity; providing, of course, that a supply of building material is at hand. When the physician wishes to increase the living protoplasm of the body, therefore, he should remember that it is more important to increase the functional activities of the cells than to furnish the body with an oversupply of food.

Among the materials essential to the building of the larger proteid molecule seem to be certain intermediate products of carbohydrate consumption—the keto-acids. This explains, possibly, the favorable influence of carbohydrates in the maintenance of nitrogen equilibrium.

We have seen that the amount of energy needed by the body depends primarily upon the work performed and the heat expended. A person lying in a warm bed, for example, expends less energy than does one who works hard eight or ten hours each day, or who is exposed to very cold weather. When excessive quantities of non-nitrogenous food are taken in the diet, a portion of the excess is decomposed into its end products, carbon dioxide and water; thus Rubner has shown that the feeding even of greatly excessive amounts of fat leads to no appreciable increase in heat production. So far as man is concerned, what constitutes such an excess is still undetermined; in all probability individual variations play an important part.

Stahelin[17] has observed in cases of tuberculosis an enormous increase in energy expenditure following the ingestion of proteids. Certain individuals do not gain weight despite a diet of extremely high caloric value. According to Grafe,[18] this is due not to a deficient absorption from the intestines, but to a greatly augmented metabolism both in the fasting condition and after the taking of food.

Disturbances in Fat Metabolism.—We have said that if large quantities of non-nitrogenous material are taken in the food, the unused excess is stored up in the body either as glycogen or as fat. The quantity of fat in the body depends, therefore, to a

great extent upon the relation that exists between the supply of, and the demand for, energy-producing material.

Different classes of foodstuffs produce different effects as regards the tendency to accumulate fat. For example, when proteids are eaten, the general metabolism is accelerated far more than when fats or carbohydrates are taken, and consequently less energy is left for storage. The question as to whether fat is ever formed directly from the proteids or not, has been settled to the extent that it is known that sugar is split off from proteids and that fat arises from sugar. At any rate, an excess of proteid material in the food would favor a retention of fat in the body, for the reason that the non-nitrogenous products of proteid cleavage may be utilized for energy. This would spare the fats and carbohydrates and allow them to be stored.

The carbohydrates of the diet that are not burned immediately are deposited in the body partly as glycogen and partly as fat.[19] That carbohydrates may give rise to fat in the body has been demonstrated repeatedly. This transformation takes place with the elimination of oxygen, which is subsequently used in metabolism. Consequently more carbon dioxide is eliminated from the lungs than corresponds to the oxygen absorbed. The respiratory quotient, or ratio of the former to the latter, may rise, therefore, to as high a figure as 1.3 during this formation of fat from carbohydrates.[20] The fat that is thus formed is rich in stearin and plamitin, but poor in olein. In what part of the body the transformation takes place is not known, though there is some evidence that it occurs in the liver.

If fat is ingested in excessive quantities, it is deposited as such in the body. The composition of animal fat is, therefore, to a certain degree, dependent upon the composition of the fats taken by the mouth. In spite of this fact, however, the body fat in man and in many animals preserves a fairly constant composition. This may be explained on the assumption that the body tends to pick certain fats out of the food for storage, or that the food commonly taken is really of a more constant composition than is ordinarily believed. Possibly the main reason for this uniformity resides in the fact that a great part of the body fat arises from carbohydrates.

The relation of the ingestion of fluids to fat

metabolism is a much-discussed and still unsettled subject. Many stout individuals drink a considerable quantity of liquids, especially of beer, and it often happens that when the latter is stricken from the diet, a loss of weight promptly follows. This result is due in part to the loss of energy that would be derived from the alcohol and carbohydrates of the beer; but it may be due in part to the lessened quantity of fluids taken. Small amounts of other drinks, such as coffee, tea, bouillon or light wine, are often taken to increase the appetite, and if these be omitted the individual may eat less and so lose weight from this cause. Although these facts are of the greatest practical importance, they have no theoretical bearing on the question as to whether or not fluids directly influence the storage or decomposition of fats in the body. Though this question has not yet been satisfactorily settled,[21] it seems worth while to review some of the evidence bearing upon it, and to call attention to some of the difficulties encountered in its solution.

It is a surprising fact that while animals are being fattened very little water is usually allowed them,[22] from which we may infer that a relatively dry diet certainly does not seriously interfere with the accumulation of fat in the body.

The question as to the effect of liquids upon the accumulation of fat in man is a difficult one to solve; for in him the only method whereby we can practically estimate a gain or loss of fat is weighing, and a difference in weight might equally well be caused by a change in the quantity of proteids, of glycogen or of water in the body. The first two of these may be neglected, practically, for the variations that they undergo are not great. The third, however, is of the utmost importance in a consideration of this question, and constitutes a considerable source of error whenever we assume that a gain or loss of weight is necessarily caused by a correspondingly great gain or loss of body fat.

Stout persons ordinarily drink large quantities of water, probably because they perspire so freely, and this water is not all immediately excreted, but is stored in part in the body. If now the patient refrains from drinking water, and takes much exercise, he loses weight rapidly. The main cause of this early loss of weight, however, is the loss of water, the result being merely a drying-out of the body.[23] Indirectly this loss of water may assist in reducing the fat in the body, for when the weight of a stout per-

son is lessened by the loss of fluids, it is possible that he will take more exercise and so consume more fat.

It will be seen from these considerations that different factors render this question a most difficult one to solve. At present we possess no conclusive evidence that the limitation of fluids directly influences fat metabolism; though such a limitation may indirectly reduce the weight of the body either by removing water from it, by diminishing the amount of food taken or by increasing the ability to take exercise.

Pathological Accumulations of Fat.—No sharp distinction can be made between pathological and physiological accumulations of fat, and it is often merely a matter of opinion as to whether a given person is too stout or not. The line separating the normal from the abnormal should be drawn at the point where the general health and the capabilities of the individual begin to be impaired. When these are affected, we are justified in speaking of a pathological accumulation of fat.

Fat tends to collect in certain parts of the body, especially in the subcutaneous tissues and the mesentery, and about the heart, the kidneys and the liver. In young animals it may also collect in the muscles between the individual muscle-fibres,[24] whereas in older animals it tends to accumulate in the above-mentioned situations.

The individual who suffers from excessive accumulations of fat gradually becomes less and less able to work. This is due, in part, to the increased weight of the body, for more exertion is required to execute the same movements. On this account, fat persons are inclined to avoid all unnecessary exertion. This being the case, their muscles tend to atrophy from disuse, and the disproportion between the body-weight and the individual's locomotive power constantly increases. The patient avoids movements because his body is too heavy; and the lack of exercise weakens his muscles so that he is less able to move. Most stout people also perspire very readily, because their thick layer of fat diminishes the amount of heat given off from the surface of the body by radiation and conduction. This sweating is very unpleasant, and furnishes another excuse for their avoiding exercise.

In Rubner's laboratory, the capabilities of lean and stout men have been carefully studied under different conditions of temperature and humidity,[25] and it has been shown that as the temperature

and humidity of the air increase the ability of stout people to work diminishes rapidly, for they quickly become overheated and perspire profusely. Their fat thus renders them less able to work and soon causes unpleasant subjective sensations from overheating.

Finally, very stout people avoid exertion because they get out of breath so easily. Their dyspnœa is due, in the first place, to the increase in abdominal fat, which limits the movements of the diaphragm; in the second place, to the additional weight of the body which necessitates more actual work for the accomplishment of the same movements; in the third place, to a weakness of the muscles or to an associated anæmia; and finally, it is due to the cardiac disturbances which are so often present in obese individuals and which have already been described (p. 43). It is thus apparent that excessively fat persons suffer in a variety of ways, partly on account of the presence of the fat itself and partly on account of the weakness of the general or cardiac musculature.

The primary cause of obesity lies in a disproportion between the energy taken in the food and the amount expended by the body. As we have just said, stout people usually show a disinclination to exercise, and this, by diminishing the expenditure of energy, favors the deposition of new fat in the body. Furthermore, many stout persons eat to excess, and the carbohydrates and fats in their diet are especially disadvantageous. In certain instances, the absorption of proteids seems to be diminished, and the patient suffers, at one and the same time, from too much fat and too little proteid.[26] Alcoholic beverages certainly tend to increase obesity. In the first place, they furnish a not inconsiderable amount of energy in the form of alcohol, and frequently also in the form of carbohydrates (beer); and, in the second place, they tend to take away the energies of the individual and so to diminish the exercise that he takes.

These causes, singly or together, are responsible for most cases of obesity. It is merely a problem in arithmetic. A certain amount of energy is taken in the form of food, a certain amount is lost as heat and work, and the remainder is stored up in the body mainly as fat. As soon as the accumulation of fat begins to deter the patient from taking active exercise, a vicious circle is established and he tends to increase in weight more and more.

The question has been raised as to whether all cases of obesity can be explained in this comparatively simple manner. Physicians certainly have the impression that not all cases are due to a simple disproportion between the energy taken in and that given out; and it seems as if many persons, in spite of abundant nourishment and little exercise, remain lean, whereas others become stout, even though they eat but little and do considerable work.

It is extremely difficult to form a judgment on this question. In the first place, it often happens that, although the patient thinks he is not eating to excess, he is really doing so. Then we have no accurate method for determining the amount of exercise that he takes. There are the most extraordinary individual variations in this respect, as can be readily imagined if we compare a nervous individual, constantly in motion and all his muscles tense, with a phlegmatic person who never executes an unnecessary movement. The energy expended by each is vastly different, even while they are accomplishing the same task. Finally, factors that influence heat losses must be considered, such as, for example, the thickness of the clothing, the temperature of the surrounding air, its moisture, etc. All these influence, to some degree, the consumption of energy in the body.

Yet, even allowing for all of them, there still remains the impression that some men exhibit an unusual relationship between the diet, the exercise taken and the fat deposited. Some children,[27] for example, show a remarkable tendency to become stout; or certain families are known for the obesity of their members; some anæmic persons tend to accumulate fat, etc. To be sure, it may be answered that when the parent eats to excess, the children learn the same habit, or that the anæmias tend to limit the amount of exercise taken, etc. Nevertheless, the impression remains that, for some unknown cause, certain individuals possess a peculiar tendency to lay on fat.

We should not, however, trust to impressions. The question is one that can be solved only by careful and exact experiments, and up to the present these have furnished no evidence which would indicate that such a constitutional tendency to obesity, in the sense of a slower rate of metabolism, actually exists. For example, Rubner has shown that, of two brothers, one stout and the other thin, the former burned up even more fat than the latter. Others have demonstrated that stout persons

consume a normal amount of oxygen and give off a normal amount of carbonic acid gas during fasting;[28] and, although the increase in heat production that immediately follows the taking of food is said to be less in stout than in thin persons, we are hardly justified from this fact alone in assuming a slower rate of metabolism in the former.

Recent studies have shown that a slower rate of metabolism actually may be present in obesity. The caloric needs in the experiments of v. Bergmann and Stähelin[29] were so small that one must assume the possibility of a constitutional adiposity. Grafe[30] has shown that a similar diminution of energy expenditure may occur also in comatose conditions.

The gain in weight that so often follows castration has been cited as an example of a constitutional change leading to obesity. It is certain that many, though not all, castrated animals and men gain in weight. We may question, however, whether this gain is directly due to the loss of a hypothetical accelerating influence of the genital organs upon metabolism, or whether the gain is not indirectly due to changes in the temperature of the individual, in his appetite for food, his desire to exercise, etc. Lüthje[31] has made a careful comparative study of the nitrogenous metabolism, and a partial study of the carbon and mineral metabolisms of castrated and normal dogs over a period of more than a year, and, finally, at the end of this time, he has determined the total composition of their bodies. As no differences could be found between the normal and pathological animals, we must conclude from these experiments that castration does not directly affect the body metabolism. Although other observers[32] have found certain differences by other methods, nevertheless it seems to me that Lüthje's experiments are the most conclusive we have. Nor have studies on castrated women cast any doubt upon the validity of his results.

This much is certain, that obesity results from a failure to consume all of the nourishment taken; but that a lessened rate of cellular metabolism also plays an important part in certain cases, has been shown by recent observations.[33]

The association of obesity with anæmia, with gout, with arteriosclerosis and with various forms of calculi, should be mentioned here, though the exact causal relation between these is unknown to us. Further-

more, when we compare the many similarities in the picture of myxœdema and obesity, we need not hesitate in attributing to a lessened activity of the thyroid gland a part in the abnormal accumulation of fat. (And, finally, various types of adiposity—adiposis universalis, dystrophia adiposogenitalis, adiposis dolorosa—have come to be regarded as manifestations in many cases of an insufficiency of the posterior lobe of the hypophysis, associated with an increased tolerance for carbohydrates. This accumulation of fat may be due to a primary hypopituitarism, or it may follow a period of increased hypophysial activity, the end stage being called by Cushing[34] dyspituitarism.—Ed.)

Pathological Changes in the Metabolism of Proteids.—As has been described, the growing child and the convalescent from infectious diseases are both able to retain some of the nitrogen taken in the food; whereas a normal individual under like circstances would soon come into a condition of nitrogenous equilibrium. Even in the above instances, however, a great excess of food is usually taken, for such individuals have an enormous appetite.

Pathological Destruction of Proteid Material.—If, as has been said, the ingestion of proteids falls below a certain limit, or if the body has no non-nitrogenous material at its disposal, and is not oversupplied with proteids in the food, then the living nitrogenous substances in the tissues must be consumed to supply the body needs. In the class of cases which we now wish to consider, however, there is a pathological consumption of the body substance, and especially of its proteids,[35] even though an ordinary amount of food be taken. If such a patient fasts, his excretion of nitrogen is considerably greater than is that of a normal individual of like weight, etc. If an attempt be made to bring him into a condition of nitrogenous equilibrium, it is often a complete failure, for as proteids are added to his diet the consumption of nitrogenous material also increases, so that the output of nitrogen remains constantly somewhat greater than the intake. In certain of these cases, however, it is possible to maintain a nitrogenous equilibrium by using enormous quantities of food.

We must not lose sight of the fact, however, that what we call a pathological destruction may be only a disturbance in the power of the body to synthetize proteids—a process which pro-

ably plays a larger rôle in metabolism than is generally supposed. And it is possible that fats and carbohydrates have an altered influence upon proteid metabolism in the pathological types of proteid destruction we are considering. For example, in certain disorders of the liver, a considerably larger amount of carbohydrates than under normal conditions is necessary to insure a proper fat consumption without an associated destruction of the body proteids.[36]

A pathological proteid destruction of this character takes place in all forms of fever, and will be referred to again in that connection. It also occurs in many patients with carcinomata[37] and other malignant tumors, in many with tuberculosis, even though no fever is present, in severe anæmias[38] and in certain intoxications, as from phosphorus.[39] Possibly, also, it is present in other conditions, such as scleroderma, lichen ruber and pemphigus vegetans. In these conditions, it is not the disease *per se* which determines the destruction, but rather some condition, as yet not understood, of the tissues themselves.

In the chronic leukæmias, even in those without fever, metabolism as a whole is increased, though proteid destruction is apparently unaffected.[40]

In the conditions enumerated, excessive quantities of fat are also frequently consumed, for the diet is often an insufficient one, but this consumption follows the ordinary physiological laws of inanition; whereas the destruction of proteids is of a pathological character. Which cells of the body suffer most from this consumption of proteids has never been determined, though one would be inclined to believe the loss falls on the same organs as it does in inanition (see p. 308).

Not all patients with carcinomata, severe anæmias or tuberculosis suffer from this increased destruction of proteids; and it would appear, therefore, that other factors are operative in these cases. In view of the fact that certain poisons, such as phosphorus, may accelerate the destruction of proteid material, F. Müller has advanced the hypothesis that toxic substances are also responsible for the increased proteid destruction in certain cases of carcinoma. These toxic substances have never been isolated, yet there is every reason to believe that this explanation is a correct one.

Only when this hypothetical poison is produced does the disease lead to a destruction of proteid material. This theory is supported by the fact that in tuberculosis and carcinoma we sometimes see toxic symptoms resembling those of diabetic coma.

In the light of our present conception that the body may build its own proteids from the simpler components of the latter, it is possible that a pathological proteid destruction may be due to a toxic disturbance of this synthetic process. As amino-acids are built up from keto-acids (an intermediate step in the combustion of carbohydrates) and ammonium salts, it is readily understood how carbohydrates may affect the elimination of nitrogen.[41]

In carcinoma, special factors play a rôle in the destruction of proteids. According to Blumenthal,[42] ulceration of the primary growth and the formation of metastases have a distinct influence upon the body proteids. Schmidt[43] attributes this to the formation of a heterolytic ferment, which under given conditions enters the circulation. Though this is still disputed,[44] Abderhalden observed certain differences in the behavior of ferments from healthy and carcinomatous tissues (see p. 186).

A pathologically increased nitrogenous metabolism is most serious, for it becomes impossible to maintain the patient's nutrition, and the loss of proteids may eventually prove fatal.

The Metabolism in Thyroid Disease.—Many patients with exophthalmic goitre manifest no peculiarities as regards their metabolism; others, however, show periods of fair to good nutrition alternating with periods of emaciation. This emaciation may occur even when the appetite is considerably increased. One of F. Müller's patients,[45] for example, weighing only twenty-nine kilos (sixty-four pounds), lost both in nitrogen and general weight, even though the diet furnished as much as sixty-eight grams of proteids per day and fifty-eight calories for each kilo of body weight. In such cases a pathological consumption of both nitrogenous and non-nitrogenous material is undoubtedly taking place in the body. Steyrer,[46] on the contrary, found no increase in nitrogen elimination or in metabolism as a whole, in cases of hyperthyroidism which were given thyroid extract. Magnus-Levy[47] observed an increased oxygen consumption in hyperthyroidism whether the individual was at rest or not, due probably to the marked motor unrest. As a rule, it is possible

to attain a nitrogenous and caloric equilibrium in these patients by giving them very large quantities of food.[48]

It is very interesting that, in Matthes's cases, the excessive consumption of proteid material disappeared after the removal of a large part of the thyroid gland, thus conclusively demonstrating that the pathological thyroid function increased the consumption of nitrogenous and non-nitrogenous material in the body. It was found, furthermore, that when the substance of the thyroid gland was administered to these patients after their operations, the excretion of nitrogen rose to what it had been previously.

The amounts of oxygen absorbed and of carbon dioxide eliminated by patients with exophthalmic goitre are greater than the normal.[49] This is in accord with the observation that after the removal of the thyroid gland from rabbits, these animals show an abnormally low "respiratory interchange of gases" when fasting; and, if thyroid substance be then administered to them, this interchange returns to the normal.[50] We see, therefore, that in certain patients with exophthalmic goitre there is an increased consumption not only of proteids but also of non-nitrogenous materials. In this last feature the metabolism differs from the increased proteid metabolism of carcinoma; and it is possible that the loss of proteids in exophthalmic goitre is merely secondary to the loss of non-nitrogenous material.[51]

The administration of the thyroid gland to healthy men or animals, either by way of the digestive tract or by subcutaneous injections, increases the bodily consumption of proteids and fats.[52] In a certain proportion of cases this loss may be covered by an abundant diet. Here again it is uncertain whether the destruction of proteids is secondary to the destruction of fats or not, though in general it would appear that the proteids are directly affected and not because of a deficiency of fats.

Metabolism, as a whole, is sometimes moderately increased after thyroid extract administration, and at other times unchanged. Hence, the loss in weight suffered by stout individuals who have been given thyroid extract cannot be due solely to a generally augmented metabolism, but must depend in great part upon the increased exercise which is prescribed.

It is not unlikely that a physiological func-

tion of the thyroid gland is the regulation of the body metabolism. At any rate, we often meet with individuals whose metabolic processes exhibit marked quantitative changes and whose thyroid glands suggest variations from the normal, not in the sense of an exophthalmic goitre. For example, an emaciation often follows the exhibition of small doses of iodin, which clinically bears a close resemblance to thyroid cachexia. Peculiar factors must be at work here, however, for iodin ordinarily does not augment metabolism.[53]

If the function of the thyroid gland be diminished below a certain point, nutritional disturbances may develop in the skin, nails, bones and other organs.[54] The skin becomes thick and immobile, owing to a collection of mucin-like material in the corium, the connective-tissue fibrils thicken and the hair falls out. Weakness of the muscles and disturbances of sensation are associated with a general loss of intelligence; and if the glands be removed from growing animals, the growth may be stunted. Metabolism in these cases is generally and markedly slowed and diminished, both as regards the destruction of proteids and the consumption of energy in general.[55] After extirpation of the thyroid, fats and carbohydrates do not reduce proteid destruction to nearly as marked a degree as they do normally.[56] In general the manifestations of thyroid insufficiency depend upon the rapidity with which the changes in its secretion have occurred and particularly upon the age of the individual.

These symptoms closely resemble those of myxœdema and cretinism,[57] conditions in which the thyroid gland is found to be diseased or absent. The variations in symptoms seen in these diseases are probably due to the varying intensity and character of the thyroid lesion, as well as to the age of the patient when the disease began. The changes in myxœdema and cretinism are to be attributed, therefore, to an insufficient function on the part of the thyroid gland. As proof of this we have the remarkable results obtained by the administration of thyroid substance to these patients.[58] It is important to remember that partially developed cases (formes frustes) of hypothyroidism, as well as of hyperthyroidism, are not uncommon among all peoples.

Exophthalmic goitre, on the contrary, is probably due to an increased thyroid function.[59] In favor of

this view are the facts that a partial extirpation of the thyroid has improved or cured many patients with this disease, and that the administration of large quantities of thyroid substance to a normal individual will produce symptoms resembling, to a certain degree, those of exophthalmic goitre.

The picture of hyperthyroidism is a variable one.[60] The individual case may be mild or severe, and its course chronic or very rapid. Of great theoretical importance is the question whether the manifestations of this disease are the result merely of a hypersecretion of the normal products of the thyroid gland or whether there is an associated chemical alteration of the latter. Though this question is still *sub judice,* it seems to me that the change is purely a quantitative one; speaking for this are the results of surgical interference, as well as the production of the characteristic symptoms in animals and in man by feeding not only extracts of the gland, but also iodin and its compounds.[61] Baumann has familiarized us with the rôle of the thyroid in iodin economy, and has shown that in certain individuals—in those particularly whose thyroids are already functionally disturbed—the exhibition even of small doses of iodin suffices to render the thyroid overactive.

The activities of the thyroid are also intimately bound up with those of the nervous system. Many cases of hyperthyroidism are of nervous origin. That the nervous system directly or indirectly stimulates the gland is a possibility, for we are still uncertain whether hyperthyroidism rests upon a primary disturbance of the thyroid gland. The glands of internal secretion are all intimately dependent upon nervous and psychic factors, and the evidence of the latter is almost a regular accompaniment of hyperthyroidism.

The pathological substratum of Basedow's disease is not specific, despite the frequency of such findings as changes in the colloid and an epithelial hyperplasia, as well as lymphoid infiltration.[62] At any rate, the clinical picture may arise in association with strumas of various types or even in the apparent absence of thyroid changes.

The symptom-complex, as we have already emphasized, is extraordinarily variable. Rudimentary forms with a few manifestations are extremely common. Personally, I am strongly convinced that from a simple goitre a series of

thyreotoxic conditions may arise, varying from the mildest to the most severe types. It is advisable perhaps, for clinical reasons, to distinguish these transitional forms, such as the Kropf-herz, though this represents merely one manifestation of the many. On the other hand, one of the characteristic evidences of hyperthyroidism—an augmented metabolism—may be absent even in severe cases of the disorder.

The origin of the various symptoms of Basedow's disease is not known. Certain factors point to increased sympathetic irritability. Furthermore, we would call attention again to the interrelationship of the ductless glands, though the weighty observations[63] reported from the Gottlieb institute relative to a non-increase of epinephrin in the blood of Basedow patients suggest caution in this respect.

There seems good reason to believe, despite the inherent complexity of the problem, that the thyreotoxicoses are susceptible of clear-cut classification; though I would discard such vague subdivisions as vagotropic and sympathicotropic,[64] and also a classification based upon the polyvalence of the thyroid substances.

The parathyroid glands are functionally distinct from the thyroids, and their complete removal from animals is followed by tetany.[65] In accordance with this experimental fact is the experience that in those clinics where the method of extirpation of the thyroid involved a simultaneous removal of the parathyroids the patients showed a special tendency to tetany. The exact way in which the parathyroids affect the nervous system is not known. (It would appear from the studies of several observers[66] that the parathyroids exert their effect, in part at least, via the sympathetic nervous system. Complete extirpation of the glands in dogs leads to a marked increase of vasomotor irritability. That this may be a result of calcium deficiency is indicated by the fact that subsequent injections of calcium salts tend to restore this irritability to its normal level.—Ed.)

The Qualitative Changes in Metabolism

Unfortunately, we know but little concerning the intermediary stages through which the various constituents of the body pass before they are finally eliminated through the excretory organs as highly oxidized products. Though it would be logical to discuss the catabolism of each substance separately, and to follow

each to its excretion, this is not possible with our present limited knowledge. For this reason, therefore, we shall merely consider, first, certain facts concerning the proteids, and, later, certain abnormal excretory products.

The proteids taken in the food are split up in the body into nitrogenous and non-nitrogenous constituents. The former probably consist of ammonium compounds; and the greater part of these are synthesized into urea, probably in the liver, and are then eliminated through the kidneys. Nitrogen is present in the urine in various forms, about eighty-five per cent. being urea, from two to five per cent. ammonia, and the remaining ten per cent. a variety of compounds of which uric acid and the purin bases form a large part.

Whether or not the proteid catabolism in the body follows the same course as it does in the digestive tract—viz., albumoses, peptones and amino-acids—has not yet been determined. Pathologically, at least, albumoses and amino-acids may be formed, for they are demonstrable in the urine, as will be shown in discussing the subject of autolysis (p. 326).

Autolysis.—If the organs of the body are kept aseptically at 37° C. for some time, their proteids undergo hydrolytic cleavage, owing to the action of enzymes that are present in the cells.[67] Albumoses and peptones have not been demonstrated as products of this "autolysis," presumably because they are so rapidly split up into amino-acids, basic substances, fatty acids, hydrogen sulphid, carbohydrates, etc. The nucleo-proteids are decomposed into proteids and the nucleinic acids, and the latter in turn into phosphoric acid and the purin bases. It is an interesting fact that the enzymes in any particular class of cells will split up the proteids of those cells more readily than they will proteids from other sources. To what extent the cleavage of proteids within the normal body resembles autolysis is not known, for normally the intermediary products of proteid catabolism, such as the amino-acids, do not appear in the urine. This last is not conclusive, however, for it is possible that the normal organism oxidizes them so rapidly that their existence is a short one. Speaking for this hypothesis is the fact that even in conditions in which large amounts of proteid are hydrolyzed (phosphorus poisoning, acute yellow atrophy of the liver) amino-acids may not appear in the urine, or, if they do, their amount is small. Albu-

moses[68] have been found by some observers in the blood of healthy individuals, but this has not been generally confirmed[69] (*cf.* p. 139).

The products of a hydrolytic cleavage of proteids are, however, excreted under pathological conditions, especially when dead cells or fibrin are left to themselves, as occurs in abscesses, in the resolving stage of pneumonia,[70] in acute yellow atrophy of the liver and in phosphorus poisoning. In these conditions, albumoses and even peptones may appear in the urine.

Since the above conditions are caused by toxic or infectious processes, the question naturally arises as to whether the hydrolytic cleavage of the proteids is due directly to the toxins or bacteria that cause the disease, or whether it is due to the action of intracellular enzymes and is of the nature of an autolysis. The former view seems rather improbable, for Müller has shown that the pneumonic exudate exhibits no tendency to undergo hydrolytic cleavage so long as but few leucocytes are present, even though the bacteria have been constantly at hand. As has already been mentioned, the tissues, even when free from all bacteria, contain proteolytic enzymes, and it seems probable that these are responsible for the abnormal decomposition in the above-mentioned conditions.

During the involution of the puerperal uterus the muscle-fibres also undergo autolysis, and the resulting products may appear in the urine.[71]

In many diseases of the liver no abnormal end-products of proteid decomposition are excreted. In other more serious and extensive hepatic conditions, various pathological substances appear, and in acute yellow atrophy and phosphorus poisoning, especially, the urine may contain albumoses,[72] or even peptones,[73] as well as leucin, tyrosin, para-oxyphenylacetic acid and lysin.[74] These substances appear to arise mainly from an autolysis of the liver cells, but in some cases the quantity in the blood is so great that they could not possibly have all originated in this manner, and some must have come from other tissues.[75]

By means of Emil Fischer's improved technic for the detection of amino-acids,[76] we have learned that these bodies are present in not inconsiderable amount in the urine even of healthy indi-

viduals.[77] They appear also in such conditions as gout, leukæmia and the infectious diseases, though not in excessive quantities.

The Formation and Excretion of Ammonia.—Normally, from two to five per cent. of the total nitrogen excreted appears in the urine in the form of ammonium salts. Under pathological conditions, however, the proportion may be greatly increased; and in acute yellow atrophy, for example, it may reach thirty-seven per cent., and in starvation even fifty-seven per cent.

An increased excretion of ammonia is not the result of an increased production of this compound within the body; for large quantities of the ammonium salts of organic acids may be taken by the mouth with only an insignificant increase in their elimination in the urine.[78] The quantity of ammonium salts in the urine is to be regarded rather as an indication of an excessive quantity of acid in the body. The ammonia normally formed in metabolism, instead of being transformed into urea, combines with the excessive acids, and is excreted by the kidneys as the ammonium salts of these acids. The body thereby retains for the most part its fixed alkalies for the transportation of carbon dioxide. Eppinger[79] sees in the differing behavior of herbivora and carnivora in respect to their ability to neutralize excessive acids, only the result of their dissimilar foods; in other words, he believes that the ammonia employed in the neutralization of acids arises not from the body proteids, but from those ingested. Indeed, the administration of large amounts of alkalies may cause a complete disappearance of the urinary ammonia. Walter[80] found that, after administering hydrochloric acid to dogs, about three-fourths of it was neutralized by ammonia in the body, while most of the remainder went to raise the acidity of the urine, and a small part apparently combined with the fixed alkalies of the blood. This last effect is serious, for the ability of the blood to carry carbon dioxide is thereby diminished (see p. 224).

An excessive excretion of ammonia is indicative, therefore, of an excessive amount of acid in the body. The amount of ammonia in the urine is increased whenever the proteids of the diet are increased at the expense of the carbohydrates, for the reason that proteids furnish an acid ash. The amount is increased, furthermore, whenever there is a pathological breaking down of

the tissues, for this is equivalent to an increased proteid catabolism. In diabetes, an excessive amount of organic acids may be formed, thus increasing the elimination of ammonium salts. Finally, an abnormal excretion of ammonia is the rule in febrile conditions[81] and may also accompany various chronic diseases, especially of the liver. In phosphorus poisoning, the output is both relatively and absolutely increased and may reach seventeen per cent.

That the increased elimination of ammonia is purely secondary has been proved by the fact that, if alkalies be administered to patients who excrete excessive quantities of ammonia in the urine, the abnormal acid in the body will be neutralized, the excessive excretion of ammonium compounds diminished and the excretion of urea correspondingly increased.

In some instances the origin of the abnormal acidity is readily determined. Mineral acids may have been taken by mouth, either accidentally or with suicidal intent. In phosphorus poisoning, the rapid destruction of cellular protoplasm liberates the sulphur and phosphorus contained in the proteid molecules, and these give rise to sulphuric and phosphoric acids in considerable quantities. In addition to these, various organic acids, such as lactic and aromatic acids, are formed in phosphorus poisoning, and this excessive acid production is sufficient to account for the increased excretion of ammonia which takes place in this condition. In many diseases, however, the explanation is not so close at hand and we must assume that organic acids are produced to account for the increased ammonia excretion.

The Production of Organic Acids.—Organic acids, especially carbonic and carbamic acids, are being constantly formed in normal metabolism. These particular acids, however, are not eliminated in ammonia combinations, for the carbonic acid leaves the body, for the most part, through the lungs, and the ammonium salt of carbamic acid can be transformed into urea in the liver. The organic acids that are most frequently eliminated as ammonium compounds are beta-oxybutyric and diacetic acids.

It is remarkable that sarcolactic acid is not more frequently found in the urine, for we know that it is normally formed in considerable quantity during muscular activity. Under such

circumstances, however, it is apparently rapidly oxidized. It probably arises from the non-nitrogenous products of proteid cleavage, although it is possible that it may also arise in part from the carbohydrates, in view of the close relationship that we now know to exist between the latter and proteids. Pathologically,[82] lactic acid has been found in the urine in cases of phosphorus poisoning, trichinosis, pernicious anæmia, severe heart disease, acute yellow atrophy and in animals during arsenical poisoning and after severe hemorrhage. Yet in none of these conditions, with the possible exceptions of phosphorus poisoning and acute yellow atrophy, does lactic acid regularly appear in the urine. In some instances, its appearance is due to a diminution in the oxidative processes within the body,[83] especially in the liver, and, in still others, to unknown causes. Ethyliden-lactic acid has been found in the urine in severe cases of diabetes, and at times propionic and acetic acids have also been found.

Of all the organic acids, beta-oxybutyric is the most important in this respect, for it appears in the urine not very infrequently, and is sometimes excreted in enormous quantities. By oxidation of this acid, diacetic acid is formed; though the process may be reversed—beta-oxybutyric acid is formed from diacetic acid by reduction—as recent studies[84] have shown. Acetone probably does not arise in the cellular metabolism proper, but rather in the lungs and kidneys, through which it is excreted, in the former case giving to the breath the characteristic "fruity" odor. The condition underlying the building of these so-called acetone bodies is known as acidosis.[85]

Normally these bodies are oxidized to carbon dioxide and water in the body, and only traces, at most, of acetone are excreted in the urine. Under various abnormal conditions, however, they may leave the body unoxidized. This may occur during hunger,[86] after anæsthesia, during a salt-free diet,[87] in many cases of diabetes,[88] and, in general, in severe states of inanition. Experimentally, beta-oxybutyric acid may appear in the urine of dogs after phlorhizin poisoning[89] and after extirpation of the pancreas, though the latter is rare. At times, some one or several of these compounds, but especially acetone, will appear in the urine without any apparent cause.[90] It is possible in these obscure cases, that it arises from the absorption of toxic substances from the intestines; yet even in the acid intoxi-

cations occurring especially in children, and associated with profuse diarrhœas, the acidosis is not intestinal in origin, but rather the result of a carbohydrate deficiency. It was formerly held that the acetone bodies might be formed within the intestinal canal, but at present there is but little inclination to refer their origin to this source. In the majority of cases, at least, they are produced during the intermediary metabolism within the body.

As beta-oxybutyric acid and its derivatives are not of regular occurrence in the conditions mentioned above, we must assume that special factors are influential. Prominent among these is a deficiency of carbohydrates, be it that the amount ingested is too small, as in starvation, or, with a sufficient supply, that it is improperly utilized, as in diabetes. The acetone bodies occur promptly in man and in the ape during starvation, and in dogs, on the contrary, very tardily. This starvation acidosis disappears forthwith if carbohydrates or even proteids in large amounts are ingested. In the latter case, the carbohydrate arising from the proteid is apparently the influential element.

Though the lack of carbohydrates is, undoubtedly, an important factor in the causation of acidosis, it is just as certainly not the sole one in all cases. In many of these there is an intermediate and as yet unknown anomaly in carbohydrate metabolism which plays the determining rôle; though in still others, the utilization of carbohydrates seems to be quite normal.

In no condition do the acetone bodies appear in the urine in such quantities as in diabetes mellitus. Our knowledge of the conditions underlying their formation and excretion is derived principally from studies of experimental diabetes in animals and of the disease in man. Acidosis is common and pronounced in phlorhizinized animals. After pancreas extirpation, on the contrary, it is decidedly less frequent. In human diabetes it may or may not be present, being most likely to occur in the very severe cases, *i.e.*, those with a low sugar tolerance. The transition from a mixed to a strict meat diet favors its appearance or intensifies it if it is already present. A diminished combustion of carbohydrates in the intermediary metabolism is, therefore, an important factor in the causation of diabetic acidosis, though not the only and determining factor. Nor does proteid

destruction play this important rôle, for Weintraub[91] has observed an acid intoxication in cases of nitrogen equilibrium and indeed of nitrogen retention.

Though the ultimate cause of diabetic acidosis is not known, it is probable that it resides in an anomaly of the intermediary metabolism of certain cells, linked, on the one hand, with a disturbed carbohydrate utilization and, on the other, with an increased consumption of fat.

The main source of the acetone bodies is still not definitely settled. In this connection, our attention is focussed upon the proteids and fats, rather than upon the carbohydrates as was formerly the case. We must assume that in some instances, at least, both proteids and fats contribute to their formation, for in cases of maximal beta-oxybutyric acid production, the nitrogen output is greatly below what we should expect if proteids were the sole source of the acid.[92]

Our knowledge of the origin of the acetone bodies has been appreciably increased in recent years both as a result of animal experiments[93] (perfusion, etc.) and of observations in severe cases of human diabetes based on the feeding of various substances.[94] These have shown that beta-oxybutyric acid represents a point of contact in the metabolism of two main food-stuffs, *viz.*, fats and proteids, in that the catabolism of both occurs via this acid. This is the more interesting because there exists an analogous point of contact in the case of proteids and carbohydrates in the next simpler oxyacid, lactic. Of the amino-acids, leucin, tyrosin and phenylalanin build oxybutyric acid; while of the fatty acids, butyric and capronic acids and their higher homologues with an even number of carbon atoms, have a similar property. Though these various observations are of great theoretical interest, we cannot enter into fuller detail, except to mention the fact that certain fatty acids of the aliphatic series—as well as substances which go over into sugars—are capable of strongly inhibiting the formation of beta-oxybutyric acid. Of such acids, glutaric is of particular interest[95] because its exhibition in phlorhizinized dogs—and occasionally in severe human diabetes—not only checks acidosis, but also the formation of sugar from proteid.

Attention has already been called to the fact that the normal organism is capable of oxidizing considerable amounts of the

acetone bodies, which is not the case in diabetes. That this process may take place in the liver is undoubted.[96]

An important question is whether diabetic acidosis is due not only to a deficient destruction of the acetone bodies, but also to an increased formation. This question involves and is identical with another, *viz.*, Does the decomposition of the higher fatty acids normally go beyond oxybutyric acid? That this actually does occur would appear from the finding of a diacetic acid formation in the normal liver. On a mathematical basis, it may be conceded that the split-products of fats and proteids are changed into oxybutyric acid; and it is known that the healthy body can easily destroy large amounts of oxybutyric and diacetic acids. Despite all of these observations, however, it remains to be proved that there is a constant construction of beta-oxybutyric acid. Indeed, there are many facts speaking against this hypothesis, among others that the amount of this acid increases in proportion to the degree of acidosis, or in other words, with the severity of the metabolic disturbance.

The Effects of an Excessive Formation of Organic Acids. Diabetic and Other Toxic Comas.—The specific action of the acetone bodies is a comparatively slight one. Acetone in large doses will produce a sort of drunkenness, similar to that caused by alcohol, and it is possible that in certain intestinal diseases of children it may cause a feeling of fatigue. The effect produced by beta-oxybutyric and diacetic acids is, for the most part, not a specific toxic effect of these compounds, but is due rather to their acid properties. However, recent studies[97] in particular tend to emphasize the specific nature of the intoxication. In virtue of their acid properties, these organic acids will combine with basic substances in the body, and tend to carry them away in the urine. In this manner they produce the symptoms of an acid intoxication (see p. 224).

In the comas that accompany diabetes, carcinoma and some intestinal diseases, large quantities of beta-oxybutyric acid are usually eliminated in the urine. The patient becomes stupid and sleepy or, at times, irritable. The temperature falls, the respirations become deep and often more frequent, and the heart's action becomes rapid.

The immediate cause of diabetic coma is unknown, but it seems to be precipitated in some instances by a too rigorous

meat and fat diet, by digestive disturbances, overwork, infectious diseases, alcoholic intoxication, etc. The symptoms are certainly very similar to those that result from acid intoxications experimentally produced; and in no other condition are such enormous quantities of beta-oxybutyric acid found in the urine as at the onset of diabetic coma. The ability of the blood to carry carbon dioxide is usually found to be consideraby diminished during diabetic coma, just as it is in experimental acid intoxications (see p. 224). These facts indicate the acid character of the intoxication.

On the other hand, in some comas complicating diabetes, no increased elimination of acids has been found. Yet such cases are quite rare, for, as a rule, the symptoms of diabetic coma are accompanied by an acid intoxication. The coma is preceded by an increased formation of beta-oxybutyric acid in the body, and large quantities of this acid may appear in the urine as the ammonium salt. During the coma, however, the elimination frequently does not keep pace with the acid formation, and consequently considerable amounts are retained in the body. Careful estimations of the amounts thus retained demonstrate that they are sufficient to give rise to coma. In some cases, it is possible to abort the coma, partly or completely, by the use of large quantities of soda, which serves to neutralize the acid in the body.[98]

Those rare cases of diabetic coma without increased acid formation are, according to Naunyn, produced by other toxic substances, which act directly upon the cerebral cells, and especially upon the cells of the respiratory centre. The exact nature of these toxic substances is unknown, but from the diversity of symptoms seen in diabetic coma it is readily conceivable that more than one cause is operative.

The Relation between Hepatic Disease and the Excretion of Ammonia.—The greater portion of the nitrogenous waste which does not serve to neutralize acids leaves the body in the form of urea. We know that the liver can convert many ammonium salts, such as the carbamates, into urea, and Minkowski's experiments on birds would seem to indicate that this is a portion of the normal hepatic function.[99] On the other hand, we are not certain that all the eliminated urea is thus formed in the liver, nor, indeed, that it is all derived from ammonium salts.

These questions are of the greatest importance, for it is possible that some relation may exist between

hepatic diseases, on the one hand, and the amount of urea formed out of ammonium salts, on the other. Not infrequently it happens that the liver is found to be diseased when large quantities of ammonia have appeared in the urine. We have seen that one cause of an increased excretion of ammonia is an acid intoxication, in which case the ammonia serves merely to neutralize the excess of acid. Is it not possible, however, that large amounts of ammonia may be excreted for the reason that the liver is so diseased that it cannot form urea out of ammonium salts? Such a serious loss of function could only result from a most extensive destruction of liver cells, if we may draw an analogy from the corresponding effects produced by diseases of the pancreas and of the thyroid gland.

An increased excretion of ammonium compounds at the expense of urea has been observed in different forms of hepatic disease, such as cirrhosis, tumors and extensive degenerations, though these urinary changes do not accompany all serious diseases of the liver.[100] Weintraub discovered that if ammonium salts were administered to patients even in the advanced stages of hepatic disease, these salts were converted into urea just as they are in healthy individuals, thus demonstrating that these patients are still able to transform large quantities of ammonium salts. Glæssner,[101] on the other hand, found in cases of extensive degenerative changes in the liver cells (cirrhosis, phosphorus poisoning, fatty liver, syphilis of the liver) that amino-acids ingested were eliminated in part as such, whereas the normal organ transforms them completely into urea. The administration of alkalies in these hepatic disorders would permit of a decision as to whether the ammonia acts as a neutralizing agent; for were this the case it would be appreciably diminished after the giving of soda. For the present, therefore, the question must be left in abeyance as to whether the increased output of ammonia in the urine in diseases of the liver is the consequence merely of an acid intoxication.

Alkaptonuria.—The tyrosin and phenylalanin groups of the proteid molecule give rise at times to the formation of dioxyphenylacetic acid (homogentisic acid). When this acid is excreted by the kidneys, the urine turns dark on standing or on the addition of alkalies, and the condition is termed alkaptonuria.[102] These urines will reduce Fehling's solution, and the condition may

be mistaken for a glycosuria. Though patients with alkaptonuria ordinarily show no other clinical peculiarities, attention has recently been called to manifestations which would indicate that there exists a profound constitutional disturbance similar, in a sense, to that of diabetes. For example, wounds may heal slowly in such patients;[103] and further, it is not unlikely that alkaptonuria is the forerunner of ochronosis[104]—a congenital condition, with, at times, a family tendency—and which is associated with changes in the joint cartilages. In this event, the severe joint disturbances observed in some cases of ochronosis might be regarded as due to the metabolic disturbance under consideration (arthritis alkaptonurica).

Although it was formerly believed that the substances giving rise to the reaction for alkapton were produced in the intestines, it now seems certain that the oxyacids concerned arise within the body during the intermediary metabolism, and that they appear in the urine because the organism is incapable of breaking down the tyrosin and alanin groups of the proteid molecule in a normal manner.

Interesting and extensive studies[105] have been undertaken to determine what must be the constitution of these aromatic oxyacids to allow of their transformation into homogentisic acid in the alkaptonuric individual. These studies point to the existence of certain steric arrangements both of the side chains and of the nucleus of the proteid molecule.[106] The subject is of particular interest in the light it throws on the normal catabolism of the aromatic amino-acids in warm-blooded animals.[107] It has an immediate bearing, therefore, upon the question as to whether alkaptonuria represents a qualitative change in intermediary metabolism, or whether the destruction of the aromatic oxyacids proceeds normally via homogentisic acid, the characteristic feature of the process being merely a splitting of the oxy-amino-acids without a breaking up of the benzol ring. Both theories have been espoused. Speaking against the first is the fact that the tolerance to homogentisic acid and tyrosin may not be the same.

The amount of homogentisic acid appearing in the urine depends in general, therefore, upon the quantity and form of proteid destroyed, the tyrosin content of the latter being the determining factor. We have yet to learn in what organ the transformation of tyrosin and phenylalanin into alkapton occurs. Proteid metab-

olism, as a whole, remains within normal bounds; the nitrogen output in particular is unchanged. All of this would indicate that there is no qualitative disturbance of proteid metabolism, but rather that the latter ceases when but half completed.

Cystinuria.[108]—In this anomaly, there exists a disturbance in the metabolism of the aliphatic amino-acids. Cystin, which makes up the greater part of the unoxidized sulphur in the proteid molecule, is eliminated in the urine because of the inability of the organism to utilize it. This condition is remarkable in that the individuals affected can burn cystin when administered as such, but are unable to metabolize the cystin group of the proteid molecule.[109]

Baumann and his pupils formerly believed that cystin was formed in the intestines, because cystinuria is frequently associated with the appearance in the urine of diamins (putrescin and cadaverin),[110] which occur in the fæces both in abnormal intestinal conditions and even physiologically in small amount. As diaminuria does not always accompany cystinuria, however, it is possible that the interdependence of the two is slight.

It seems unlikely that the diamins are entirely of intestinal origin. A comparison of the metabolic processes in cystinuria with those concerned in the catabolism of the aromatic amino-acids, points to this origin as being in the intermediary metabolism, particularly in the liver, where cystin is normally converted into taurin. Recent studies show that leucin and tyrosin among other amino-acids may be excreted.[111] The cystinuric individual can utilize neither the monamino-acids in his food (tyrosin, asparagin), nor the diamino-acids; the latter he excretes as diamins. The degree of the disturbance, however, varies with different individuals, for some can burn both the endogenous and exogenous amino-acids.[112] Important accessory factors, therefore, are the amount of amino-acids occurring in the intermediary metabolism, as well as the tissue in which the latter is to occur. Cystinuria, therefore, would appear to be a constitutional anomaly closely related essentially, to alkaptonuria.

The presence of cystin stones in the bladder may cause disturbances in such individuals.

The Adrenals. Addison's Disease. Epinephrin.—Addison's disease is generally associated with changes, primary or secondary, in the adrenal glands;[113] though, on the one hand,

cases are observed with normal adrenals, and on the other, extensive changes may involve these organs without producing manifestations of the disease. I shall not go into a discussion of these problems, first, because it would carry us too far, and, further, because our knowledge rests upon too insecure a footing. In my opinion, it can only be said, on the basis of the best observations, that the Addison symptom-complex and disease of the adrenals are intimately related, probably in the way of a diminished function of the latter. It is not a question of a decreased activity of the adrenal medulla and thereby of a lessened production of epinephrin, because the latter arises from all parts of the chromaffin system. v. Neusser and Wiesel, in view of this fact, regarded the disease as due to a constitutional weakness of the entire chromaffin system. This is an interesting hypothesis, explaining as it does those cases of Addison's disease with intact adrenals; for, in view of the close relation existing between the chromaffin and the sympathetic nervous systems, we might assume that there exist changes in the chromaffin cells outside of the adrenals or changes in the secretory nerves. In some cases of Addison's disease, however, the entire chromaffin system seems quite normal; and, furthermore, there are observers who look upon changes in the adrenal cortex as the cause of morbus Addisonii.

The interrelationship of the medullary and cortical substances of these glands is still undetermined despite the tremendous amount of study devoted to the subject. In my opinion, if one is to hold fast to the etiological significance of adrenal disease in the Addison symptom-complex, he must assume that the medulla and cortex are both involved.

The function of the cortex is not known. On the other hand, an epinephrin deficiency or a diminished sympathetic activity falls short of explaining even the majority of the manifestations of this disease. The diminished arterial tension ordinarily observed in these cases is readily explained on an epinephrin deficiency. But the prostration and lethargy, the muscular weakness, the anæmia and the gastric disturbances are in part, at least, not due to this cause. Some observers do not look upon the pigmentation as an integral feature

of the condition; others attribute it to changes in the sympathetic system. Biedl's theory that the mother substance of epinephrin is converted directly or indirectly into the Addison pigment is an interesting possibility.

(Among those who regard an insufficiency of the adrenal cortex as the cause of the characteristic asthenia of this disease are Biedl and Loewi. The former bases his opinion upon extirpation experiments in animals in which the cortex and medulla are separate; the latter upon cases of Addison's disease in individuals in whom only the cortex was found insufficient. Crowe[114] has recently added a convincing extirpation and ligation experiment to the evidence.

The views as to the function of epinephrin have undergone a considerable change in the past few years. It is generally agreed, in the first place, that epinephrin is a product of the medullary substance of the adrenals; that it acts only upon structures possessing a sympathetic innervation, selectively stimulating, in all probability, the so-called myoneural junction or terminal receptive substance; and that it exerts its characteristic activity in very high dilutions. The most recent studies[115] would indicate that epinephrin is not present in the blood under ordinary conditions, but, on the contrary, is poured out only in periods of emergency.

The recent work of Cannon and his co-workers has given us an entirely new conception of the significance of epinephrin. According to Cannon, epinephrin plays a definite rôle in enabling the individual to meet successfully the emergencies of life. Various emotions—pain, fear, anger, etc.—cause a reflex secretion of epinephrin and assist in the execution of the physical counterparts of the emotions, *viz.*, combat, flight, and so on. As the muscles are chiefly concerned in these bodily activities they are assumed to benefit to the greatest extent in the epinephrin discharge. The inhibition of intestinal peristalsis causes a shifting of blood from the bowel to the muscles, as does also the constriction of the splanchnic and cutaneous vessels. The hyperglycæmia consequent upon epinephrin discharge would furnish the muscles with the needed additional food-supply. More oxygen for the crisis is supplied by a dilatation of the bronchioles. Furthermore, the efficiency of fatigued muscle is greatly improved by epinephrin;

and, finally, within certain limits, the coagulation time of the blood is diminished.

In contrast with this physiological conception are the experimental results due to the injection of epinephrin in pharmacological doses. There are many facts, for example, indicating that epinephrin is not concerned with a permanent hypertension and with arteriosclerosis.[117] Among these are the limited capacity of the adrenals to manufacture epinephrin; the fact that epinephrin in sufficient amount to maintain an augmented arterial tension would at the same time paralyze intestinal activity; the fact that glycosuria appears before a rise in blood-pressure; and, finally, that the anatomical changes observed in the vessel-walls after repeated injections of epinephrin differ in many particulars from those seen in arteriosclerotic conditions in man.—ED.)

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CHAPTER VII

DISTURBANCES IN CARBOHYDRATE METABOLISM. DIABETES

In this chapter we shall limit our discussion to dextrose, or grape-sugar; for although other sugars, such as lævulose [1] and pentoses,[2] may appear in the urine, the meaning of these findings is not yet sufficiently clear to be discussed in connection with dextrose.

The cells of the body that use dextrose, especially the muscle-cells, take it out of the blood; yet the amount in the plasma remains nearly constant, for whenever the percentage falls below the normal, new sugar is supplied to the blood, mainly from the glycogen store in the liver. The liver glycogen is derived, for the most part, from the carbohydrates, and, to a lesser extent, from the proteids taken in the food.[3] The sugar that is absorbed from the intestines goes to the liver by way of the portal vein, where it is converted into glycogen by a process of dehydration and polymerization. The non-nitrogenous products of proteid cleavage may also be converted into glycogen, by a synthetic process;[4] and, as there can no longer be any doubt that a complete splitting of the proteid molecule occurs in the intestines, it is reasonable to assume that this synthesis of glycogen likewise takes place in the liver. The latter acts, therefore, as a store-house for carbohydrate material, holding it back when it is present in the blood in excess, and giving it out when the percentage falls. The muscles likewise are capable of storing sugar.

In a healthy man, the sugar in the blood varies but little, the quantity remaining constantly in the neighborhood of 0.1 per cent. If, for any reason, more than this is present in the general circulation without being immediately consumed, it is eliminated by the kidneys, and the urine then contains more than the trace of dextrose normally present.

Alimentary Glycosuria.—As we have said, the liver possesses the property of removing from the portal blood any excessive quantity of sugar that may be present there. If, for example, a limited quantity of dextrose be injected into the portal vein, the excess disappears from the blood; whereas, if the same quan-

tity be injected into a systemic vein, the percentage in the general circulation is increased and sugar is excreted by the kidneys.

Yet, when very large amounts of dextrose are taken by mouth and are absorbed from the intestinal canal within a short space of time, the percentage in the blood may rise above the normal, either because the liver cannot hold all the sugar coming to it through the portal vein, or because some sugar reaches the general circulation through the lymphatics without traversing the liver. In keeping with this latter hypothesis is the markedly lowered tolerance exhibited by dogs with an Eck fistula.[5]

Under such circumstances, dextrose may be excreted by the kidneys, a condition that is spoken of as alimentary glycosuria.[6] The quantity of sugar that must be taken by mouth in order to produce an alimentary glycosuria varies in different individuals, though it is apparently constant for the same individual. It does not necessarily follow, however, that a certain person is in an early stage of diabetes merely because he passes dextrose in the urine after taking a relatively small quantity by mouth. Yet such may be the case. Minkowski has shown, for example, that whereas the removal of the whole of the pancreas is followed by a diabetes, the removal of a part may cause merely an inability to take much sugar in the food without having it appear in the urine. Furthermore, clinical experience has demonstrated that in some cases a marked alimentary glycosuria gradually passes over into a true diabetes mellitus. In still others, on the contrary, it would appear to be quite without significance.

The occurrence of an alimentary glycosuria in a healthy man is greatly favored by alcoholic drinks, and especially by the ingestion of large quantities of beer.[7] It is impossible to say why this should be so, and whether the effect, in the case of beer, is to be attributed more to its alcohol or to its maltose. Muscular exertion and heating of the body, on the contrary, tend to diminish the excretion of sugar in alimentary glycosuria, just as in true diabetes.[8]

Lactose may also appear in the urine after excessive quantities have been taken in the food, but it appears there more frequently because it has been resorbed from the mammary glands of nursing women, owing to a stasis of milk. Some special factor seems to favor its excretion in these cases, for the amount absorbed

would appear to be too small to give rise to an ordinary alimentary glycosuria.

Many studies have been made relative to the ease with which an alimentary glycosuria may be produced in different diseases. These investigations, unfortunately, are not based upon conditions as found in a normal individual, for the patient is generally in the fasting state, and is given large amounts of pure dextrose. Despite this, such patients rarely exhibit an alimentary glycosuria; nor is it generally true that individuals with hepatic disease are especially prone to show such a glycosuria,[9] at least when dextrose is given; though it is a fact that a lævulosuria is more readily produced in similar conditions.[10] I should advise caution, however, in assuming the existence of a disordered liver function from the appearance of such a glycosuria, for we have learned, beyond question, that the specific activity of an organ—and this applies particularly to the liver—may persist even though the major part of its cells be destroyed or severely damaged.

In phosphorus poisoning, however, and thyreotoxic states, sugar passes into the urine with particular ease. Certain observers have interpreted the thyreotoxic form as an epinephrin glycosuria and as representing an increased stimulation exerted by the thyroid gland upon the chromaffin system.[11] This needs further confirmation, however. Alimentary glycosuria occurs, further, in many cases of hysteria and neurasthenia, in the traumatic neuroses and in the infectious diseases. In the latter, and also in cachectic states, the mere ingestion of starch may lead to a similar result. These various observations show how conservative we must be in interpreting such transitory and etiologically uncertain glycosurias.

Phlorhizin Glycosuria.[12]—Phlorhizin is a glucosid, *i.e.*, it is capable of being split up into dextrose and a proteid radicle, the former component representing about forty per cent. of the whole. The glycosuria following its administration is peculiar in that it is probably not accompanied by an increased percentage of dextrose in the blood. Though certain observers[13] have found a hyperglycæmia in this condition, the majority have noted no such increase in the blood-sugar, but rather a diminution; and, indeed, no increase was noted

even after removal of the kidneys. Pflüger explains these diverse findings on the basis that in the blood-sugar determinations no distinction was made between free sugar and sugar combined loosely with colloids, only the former taking part in the phenomenon. This hypothesis can scarcely be accepted, however, because the sugar of the blood is actually in solution.[14]

It is possible that a phlorhizin glycosuria, being unaccompanied, as is generally held, by a hyperglycæmia, is due to toxic changes in the renal cells which have deprived them of the power of holding back sugar. Another, far less likely, explanation is that the phlorhizin loses its sugar radicle (phlorose) in the kidneys and that this is at once converted into dextrose and eliminated, while the residue of the phlorhizin molecule (phloretin) combines once more with sugar and the process is repeated. The amount of dextrose that appears in the urine after phlorhizination, however, is so great that it cannot be accounted for by a mere splitting off of the glucosid; and, furthermore, it is certain that the administration of this substance causes an actual removal of dextrose from the body.

In phlorhizin poisoning, the sugar excreted is derived, first of all, from the glycogen of the liver, which early disappears. It seems certain that it is also derived from the proteids of the body, for it is known that glucose continues to be excreted in phlorhizin poisoning, even though the animal be fasting and its liver presumably free of glycogen. The proteid decomposition is accelerated owing to the failure to consume carbohydrates; and even beta-oxybutyric acid may be excreted. If phlorhizin be given to fasting animals, a fatty degeneration of the liver is produced, which can be prevented if the animal be fed on proteids or carbohydrates. At times, the amount of sugar excreted after taking phlorhizin is so great that it seems as if it must be formed in part from the fats of the body,[15] a possibility that will be considered in another place (p. 351).

Renal Diabetes.—The glycosuria of phlorhizin poisoning, therefore, is characterized by the fact that the amount of sugar in the blood is not increased; and it seems probable that in this condition, as well as in certain cases of marked diuresis, the resulting glycosuria is due to an inability on the part of the

renal cells to hold back the sugar normally present in the blood. Little is known about such conditions in man, but recent observations have tended to show that glycosuria may result from just such a renal insufficiency. To these cases has been given the name of renal diabetes. Lüthje[16] has shown that the sugar was present in the blood of his patient in less than the normal quantity, thus demonstrating that the glycosuria was due to some abnormal permeability on the part of the kidneys toward dextrose. Neubauer,[17] on the other hand, has observed hyperglycæmia without glycosuria in cases of nephritis with hypertension. The amount of sugar excreted by such patients is independent, to a great extent, of the amount taken in the food; yet this is not especially characteristic of renal diabetes, for the same is true of certain forms of diabetes mellitus.

Epinephrin Glycosuria.—An increase in the percentage of sugar in the blood occurs also when epinephrin in large amounts is introduced into the circulation.[18] Epinephrin is supposed to "mobilize" sugar. The amount of the latter entering the blood is directly proportional to the amount of epinephrin present, and is dependent, furthermore, upon the size of the animal's glycogen store; for with a diminution of the latter, larger amounts of epinephrin are required to mobilize the same amount of sugar. As epinephrin is capable of causing a considerable increase in the degree of proteid destruction in fasting animals,[19] it is evident that a glycosuria (and a storing up of glycogen[20]) tends to occur also in such animals. The blood constantly contains epinephrin, which acts, it may be, to regulate the vascular tonus. It is also very likely that the sugar-content of the blood is similarly under the influence of epinephrin and in turn of the sympathetic nervous system. (For the most recent studies relative to the function of epinephrin and to the interpretation of the symptoms of Addison's disease, the reader is referred to the preceding chapter, p. 336.—Ed.)

Transient Glycosurias.—Glycosurias lasting only a few hours or days[21] have been observed after various intoxications, infections, injuries and diseases of the central nervous system.

Of these transient glycosurias, the best studied is that which results from a puncture of a certain limited area

in the floor of the fourth ventricle of animals. In these cases, the appearance of sugar in the urine is always preceded by an increase in the amount present in the blood, and it is favored by a large store of glycogen in the liver. If glucose be injected into a mesenteric vein in these animals, it is not taken up by the liver as it normally should be, but passes into the general circulation and is then excreted by the kidneys. If the splanchnic nerves be cut, or if the liver be removed, a puncture of the fourth ventricle has no effect upon the urine; while the extirpation of the suprarenals likewise prevents a piqûre glycosuria.[22] Furthermore, after puncture of the ventricle, the amount of epinephrin in the serum has been found increased,[23] though this needs confirmation for the plasma. All these facts seem to indicate that the glycogen of the liver is the source of the excessive amount of sugar in the blood and that the puncture causes the glycosuria by influencing the glycogenic function of the liver via the adrenals, epinephrin and the sympathetic system. This would point to the action of the same mechanism both in piqûre and in epinephrin glycosurias, the former being of central origin, the latter peripheral. Epinephrin, for instance, causes a glycosuria after the splanchnic nerves have been cut.[24] Eppinger, Falta and Rudinger have made the interesting observation that the glycosuria of animals from which the pancreas has been removed is increased by the injection of epinephrin.[25]

(Our knowledge of the position of the hypophysis[26] in carbohydrate metabolism is at best fragmentary. According to certain observers (Borchardt), injections of the whole gland extract in rabbits usually cause a glycosuria; while Cushing was able almost without exception to produce a glycosuria—with hyperglycæmia—in rabbits, by intravenous injections of posterior lobe extracts and even of cerebrospinal fluid (assumed to contain the secretions of the posterior lobe). These various results have not been confirmed by all observers.

Cushing believes the following interpretation of the rôle of the hypophysis in carbohydrate metabolism to be permissible: "Normal posterior lobe activity is essential to effective carbohydrate metabolism. An intravenous injection of posterior lobe extract produces glycogenolysis . . ., [whereas] a diminu-

tion of posterior lobe secretion occurring in certain conditions of hypopituitarism—whether experimentally produced or the result of disease) leads to an acquired high tolerance of sugars . . . . ."

The glycosuria frequently noted in cases of acromegaly and gigantism, according to this conception, would be due to the pressure of a hyperplastic anterior lobe upon the posterior lobe, causing first stimulation and later cessation of the secretion of the posterior lobe.

The mechanism of hypophysial glycosuria is not well understood. It might be assumed to reside in a primary disturbance of the pituitary body, or on the other hand, to act via the nervous system or other internal secretions, *e.g.*, epinephrin and the sympathetic system. It is possible, however, that the functional disorder of the hypophysis is only a co-ordinate part of a more general disturbance of endosecretory activity.—Ed.)

Our recently acquired knowledge of the conditions underlying epinephrin glycosuria have thrown considerable light upon the nature of piqûre diabetes; and it is possible that we shall be able to correlate the different non-diabetic glycosurias by the variations in the blood-sugar and in the glycogen content of the liver, as well as by the results observed when the splanchnic nerves are severed.

Diabetes Mellitus

Diabetes mellitus is characterized by a glycosuria that is not due to any of the above-mentioned causes, and especially not to the ingestion of large amounts of grape-sugar. Usually, the dextrose is constantly present in the urine, though it may be found only periodically. In some cases of diabetes, lævulose and pentoses also appear in the urine. The glycosuria of diabetes mellitus always results from an excessive amount of sugar in the blood, a hyperglycæmia; instead of the normal percentage of about 0.1, it may rise even to 0.7 per cent. On the other hand, the contention of F. Müller that the behavior of the kidneys in diabetes needs further study is a sound one.[28] For example, in dogs, after pancreas removal, there may be a considerable hyperglycæmia without a glycosuria, and a number of similar observations have recently been reported in human diabetes.[29] Possibly the

total amount of sugar passing through the renal vessels is of more importance in determining its appearance in the urine than is the percentage present. Indeed, in the light of present knowledge, one may well ask whether hyperglycæmia actually plays a determining rôle in the causation of glycosuria.

If one accepts a hyperglycæmia as the *sine qua non* of the diabetic glycosuria, he must assume the existence of a renal impermeability[30] for the many cases in which there is an increase in the percentage of glucose in the blood unaccompanied by its appearance in the urine. As a matter of fact, it has been experimentally shown that the permeability of the kidneys for sugar may be raised or lowered by means of certain toxins.[31] In man, however, it would seem more likely that the kidneys are more or less unaffected by the percentage of sugar in the blood, rather than that the absence of a glycosuria in hyperglycæmic states is the result of a diminished renal permeability. It is possible, though, that diabetes does cause specific alterations in renal function, in view of the fact that it is known to injure the renal epithelium.

Mild and Severe Diabetes; Derivation of Sugar from Proteids and Fats.—In the milder forms of diabetes, sugar does not appear in the urine if no carbohydrates, *i.e.*, sugars, starches, etc., are taken in the food. Great individual variations exist as to the quantity of carbohydrate material that must be taken in order to produce glycosuria. On the one hand, a patient may be able to take one hundred and fifty grams or more of starch in twenty-four hours, without suffering from glycosuria; while, on the other, a glycosuria may result when only twenty-five to thirty grams are taken. The essence of a correct diabetic therapy resides in the effort to determine the individual's tolerance; and this is done by sparing, as far as possible, the mechanism of sugar metabolism.[32] Not all carbohydrates show the same tendency to cause glycosuria in these patients,[33] and many, for example, will tolerate lactose in the food even better than starch.

The mild form of diabetes is distinguishable from alimentary glycosuria by the fact that starch is not tolerated; for, so far as we know, a mere excess of starch in the diet of a normal individual never leads to the excretion of an abnormal quantity of sugar in the urine. Possibly, however, exceptions do occur to this rule, notably in the case of the infectious diseases.

In the more severe forms of diabetes, sugar is excreted in the urine even when no carbohydrates are taken by mouth, and in some—the most severe—cases the glycosuria continues even when the patient is fasting. In these cases, the sugar may come either from the glycogen of the ingested meat and from that arising in the abnormal diabetic metabolism, or it may come from proteids or fats.[34] The origin from the glycogen has not been disputed, but observers have not always been agreed as to the part proteids and fats take in the formation of sugar.[35] It is now generally accepted that sugar may arise from fats[36] and proteids or from both. Proteid is a more fertile source because it undergoes a more complete splitting, even in the intestines, than does fat.

Particularly interesting is the intolerance of certain diabetics to proteid foods. Naunyn, especially, has shown that many diabetic individuals become sugar-free only if their proteid intake is kept within definite limits. Certain patients cannot tolerate an increase in their proteid quota as readily as the ingestion of carbohydrates.[37] This would seem to indicate that the metabolic fault is situated where the keto-acids are normally burned, or built up into sugar-like bodies after the splitting off of ammonia.

It was formerly believed that this distinction between mild and severe cases of diabetes was a sharp one, and that it rested upon fundamental differences in the tissues. In the mild cases, the body was unable to assimilate carbohydrate material introduced as such, but was able to consume the carbohydrate molecules split off from the proteids; whereas, in the severe cases, neither could be utilized. Yet we now know that no such sharp distinction can be drawn;[38] that the one condition shades into the other; and that, finally, the body may be able to consume a considerable proportion of the carbohydrates taken in the food, even though the diabetes is so severe that glycosuria persists during fasting.[39] Notwithstanding these facts, the above distinction has a certain clinical value; and a case of diabetes can hardly be considered a mild one if the body is unable to assimilate a given amount of carbohydrate material in the food without the excretion of sugar in the urine.

The Glycogenic Function of the Liver in Diabetes.—The immediate cause of the glycosuria in human diabetes resides, according to present conceptions, in a hyperglycæmia, which is the result in turn of an inability on the part of the liver to polymerize the sugar it receives and to store it as glycogen. The lessened efficiency of the liver, in this respect, varies considerably in different cases, and upon this fact depends the variable tolerance to carbohydrates of different patients. The glycogenic power of the liver is never completely lost; as a rule it is raised when increasing amounts of sugar are carried to the organ, *i.e.*, ingested; though, infrequently, in cases of mild diabetes, the excretion of sugar is more or less independent of the amount of carbohydrates in the food.

We have already called attention to the fact that variable amounts of carbohydrates must be taken by different diabetics to cause the appearance of sugar in the urine, and that no single factor has so great an influence in raising the assimilative capacity as sparing the mechanism of sugar metabolism. Thus, a diabetic who to-day can tolerate one hundred grams of white bread, may, in the course of a few months, if kept within his tolerance limit, be able to assimilate one hundred and twenty to one hundred and forty grams with no ensuing glycosuria. This is an answer to the skepticism still expressed occasionally as to the value of a dietetic therapy in diabetes.

Certain diabetics are better equipped to take care of lævulose, and starchy foods which are converted into lævo-rotatory sugars, than of dextro-rotatory carbohydrates. We must not generalize too widely in this particular, however, for even among diabetics with a relatively high tolerance for ordinary starches, there is no uniformity in their ability to handle lævulose; and in the severe cases with a low tolerance, particularly when acidosis is present, lævulose is no better borne than dextrose.[40] The crux of this matter is that every type of carbohydrate used in a diabetic for the first time is well taken care of for a short period, irrespective of the steric grouping of its molecules.

In regard to the question as to whether the diabetic builds more sugar than the normal individual we can answer in the negative for the milder cases;

for every condition is satisfied by the assumption that the blood contains more than its normal percentage of sugar simply because the liver cannot store it as glycogen. In another place we shall consider whether the tissues are able to burn the excess of sugar carried them by such blood.

Certain severe cases, on the other hand, persistently excrete more sugar than can be accounted for by the carbohydrates in their food. Even on a strict proteid and fat diet such individuals lose large amounts of sugar. As we have noted, this sugar-excess is derived from proteids and to a lesser degree from fats. If one is of the opinion that the formation of sugar from proteids is physiological, he must distinguish sharply between diabetics who can assimilate proteids and those who cannot. For there are, undoubtedly, patients who tolerate enormous quantities of proteids, yet who excrete sugar after the ingestion even of small amounts of bread. One can only conclude that the behavior of the tissues to exogenous sugar is different from that to endogenous. The distinction has a practical bearing upon the origin of acidosis (see p. 330).

At any rate, in these severe cases, the liver is unable to store glycogen from proteid sugar any better than that from ingested carbohydrates, and the result is in both cases a hyperglycæmia and a glycosuria. Thus the liver occupies the foreground in both, though it is not improbable that other tissues, such as the muscles, are co-ordinately involved.

The Consumption of Sugar in Diabetes.—We now come to the question as to whether the diabetic body is able to burn sugar normally. Investigations on the respiratory interchange of gases have furnished evidence that the oxidation of sugar in certain diabetic patients is diminished.[41] We know that when carbohydrates are completely burned, the volume of carbon dioxide given off is equal to the volume of oxygen consumed; *i.e.*, the respiratory quotient is 1.0. For the combustion of proteids and fats, however, relatively more oxygen is necessary; and, in the case of the higher fats, the ratio of carbon dioxide to oxygen is about 7 to 10 or 0.7. When carbohydrates are the main source of energy to the body, therefore, the ratio between the carbon dioxide given off and the oxygen absorbed approaches 1.0; whereas when fats and proteids furnish most of the energy,

this ratio falls. It has been found that diabetic patients upon an ordinary mixed diet show a lower respiratory quotient than do normal individuals upon the same diet. From this fact it may be inferred that, in spite of the large amount of glucose circulating in their blood, the utilization of carbohydrate material by diabetic patients is deficient, and that most of their energy is derived from fats and proteids. Abnormally low values, *i.e.*, below 0.74, are to be explained in part by a co-existing acidosis and in part by a conversion of proteids and fats into sugar. Indeed, the degree of reduction of the respiratory coefficient may be looked upon as an index of the severity of a particular case.

It appears, also, that this change in the respiratory quotient is more marked in the severe than in the mild forms of diabetes; in other words, the former burn less sugar than the latter. This view is further supported by the effect that muscular exercise and fever have upon the excretion of sugar. In the milder forms of the disease, muscular exercise tends to diminish the glycosuria, apparently because the body utilizes the sugar circulating in the blood. In the more severe cases, on the contrary, muscular exercise exerts but little effect upon the glycosuria, for the body can utilize comparatively little sugar. In dogs whose pancreas has been completely removed, muscular exercise does not reduce the sugar excretion, but after a partial removal, it regularly diminishes the glycosuria. Hence, the pancreas, or at least a part of it, is essential to the combustion of sugar.

Thus we see that there is not only an insufficiency of the glycogen reservoirs in diabetes, which permits an excess of sugar to enter the circulation, but that there is, in addition, a lessened ability on the part of the body to burn the sugar. If the former alone were true, the respiratory quotient would increase in proportion to the amount of carbohydrates ingested, just as in health, for despite the sugar loss the blood continues to carry it in excess.

The nature of this lessened capacity for consuming sugar is not well understood. Unfortunately, we know little concerning the manner in which sugar is normally utilized in the body, or concerning the intermediary stages, such

as lactic acid or glycuronic acid, through which it may pass. There seems to be no general diminution in the oxidative ability of the body, for such substances as benzene, lactic acid, fat and frequently even lævulose, are consumed normally. Diabetes consists rather in a specific limitation of the ability to consume dextrose; and it seems as if the diabetic body fails especially to initiate the combustion of this sugar. Nor is this all. Normally, carbohydrates can be converted into fat in the body, but in diabetes this power is diminished or lost.

We are acquainted with at least one factor that is necessary for a proper combustion of the sugar in the body. This is the pancreas.[42] If this gland be extirpated from dogs, their ability to burn sugars is certainly diminished. The same holds true for carnivorous birds and for reptiles and amphibia. When about twenty per cent. of the pancreas is left at an operation, an alimentary glycosuria or a diabetes of the milder type may result; whereas, if the whole gland be excised, a diabetes of the severe type is the consequence.

There exists still a considerable diversity of opinion, even among the most competent investigators, as to the conditions essential to the causation of pancreatic diabetes, and as to the significance of its clinical manifestations.[43] A possible explanation of certain conflicting results resides in the difficulty of completely removing the pancreas, even when this is the object sought. The significance of the duodenum in this type of diabetes has also received considerable attention. In rana esculenta extirpation of the duodenum causes an even more severe diabetes than does pancreas removal; this is not the case, however, in warm-blooded animals.

Lüthje[44] has shown that if, in a fasting animal, a portion of the gland be left, the initial glycosuria will completely disappear in the later stages of starvation, and the percentage of sugar in the blood will return to normal. We must conclude, therefore, that in this form of diabetes it is still possible for an animal to consume sugar. The consumption is greater when the external temperature is high than when it is low.[45]

The full significance of the pancreas in the mechanism of sugar metabolism is still unsettled.[46] The most likely interpretation hinges on the conception of an

internal secretion. Cohnheim believes it necessary to assume the combined action of such a secretion and of muscle extract. Pflüger, on the other hand, emphasizes the importance of the nervous system in the mechanism.

Glycosuria may be produced not only by extirpation of the pancreas, but also by removal of the salivary glands and of the thyroid.[47] Furthermore, the hypophysis (see p. 348) and the chromaffin system play a part in sugar metabolism; and we have already referred to the glycosuria produced by the injection of epinephrin (see p. 347). Loewi[48] has made the interesting observation that the instillation of a drop of epinephrin into the conjunctival sac of animals whose pancreas has been removed causes a mydriasis, and that the latter does not occur in normal animals. This has been noted also in certain cases of human diabetes probably of pancreatic origin, as well as occasionally in hyperthyroidism. The inference to be drawn from the foregoing is that the pancreas inhibits the sensitiveness to epinephrin of certain organs of sympathetic innervation, whereas the thyroid augments this sensitiveness. Eppinger, Falta and Rudinger[49] have studied the interrelationship of the pancreas, the thyroid and the chromaffin system with respect to proteid and carbohydrate metabolism, and have shown a complicated interaction of these organs, in part stimulative, in part inhibitory. Possibly, certain cases of human diabetes may be explained on the basis of such an interaction.

The liver has recently not received the attention it deserves as a factor in diabetes. Newer work has again focused our attention upon this organ, and properly too, because of its intimate relation to other glands, particularly the pancreas.

Finally, as regards the pancreas, we must ask whether the secretions of the cells of Langerhans alone are of importance in sugar metabolism, or whether the pancreatic cells in general share this function. Observers are not unanimous on this point.[50] It would appear, however, from the comprehensive studies of Weichselbaum[51] that a painstaking examination will show striking pathological alterations in the islands of Langerhans in all cases of human diabetes.

The Etiology of Diabetes.—The tendency to acquire diabetes may be inherited, not alone from parents that have had the

disease itself, but also from those who have had gout, obesity or nervous disorders.

Diabetes sometimes follows severe cerebral concussions and injuries, as well as violent fright and other psychic traumata. Arteriosclerosis and syphilis are frequently associated with diabetes, though we do not know whether they cause it by their action upon the cerebral structures or not. Definite anatomical lesions of the brain, especially when situated in the neighborhood of the fourth ventricle, undoubtedly can produce diabetes, though this is a very rare event.

At times, diabetes is accompanied by diseases of the liver or pancreas. The condition of the pancreas in diabetes is of especial interest on account of the glycosuria produced by an extirpation of this gland in animals.[52] Even the older investigators occasionally noted changes in the gland in cases of diabetes. If the pancreas is completely destroyed by disease, without leading to death within the first twenty-four hours, diabetes always develops. Primary carcinomata of the pancreas, however, may completely destroy the gland without producing diabetes, apparently because the carcinoma itself retains some of the functions of the normal tissues. We have already noted Naunyn's analogous observation, *i.e.*, that a carcinoma of the liver may secrete bile. It is our opinion, based on Weichselbaum's studies, that typical and severe cases of diabetes are due in all instances to lesions of the Langerhans islets.

Effects of Diabetes Upon the Body.—In diabetes, a certain proportion of the energy taken in the food is not utilized by the body, and it is necessary, therefore, to cover the loss by more abundant nourishment. Even in severe forms of the disease, the loss of carbohydrates may be covered by the administration of large amounts of fats and proteids, providing, of course, that the gastro-intestinal canal can absorb the necessary amount of material. Fortunately, this is usually possible and only rarely is absorption markedly reduced in diabetes.[53] The greater an individual's need for energy, the more difficult will it be to maintain his nutrition when his ability to utilize carbohydrates is lessened. Yet the combined skill of physician and cook will often accomplish wonders in this respect. If the diabetic patient absorbs sufficient nourishment, his

metabolism does not, as a rule, differ from that of a healthy individual upon the same diet. If it is impossible to furnish sufficient energy to him, his fat and body proteids are consumed, just as are those of a healthy individual during partial starvation. Some diabetics seem to consume the proteid material in their bodies with abnormal rapidity.[54] But this is probably due to the fact that diabetics, as has been experimentally demonstrated, need more proteid food to maintain their nitrogen equilibrium than do normal individuals, and that if this added quota is not forthcoming they must consume their own proteids, especially since they cannot burn carbohydrates and thus spare proteids. From what has been said, it will be seen that in the more severe forms of diabetes, malnutrition frequently develops; for the patient is either unwilling or unable to take a sufficient quantity of fats and proteids to cover his total needs, and, in addition, his consumption of proteid material is sometimes abnormally rapid.

The metabolism in diabetic patients frequently shows other peculiarities as the disease becomes more advanced. Various organic acids, especially beta-oxybutyric and diacetic acids, are formed in the body. Indeed, they are produced in such quantities in no other condition as in some cases of diabetes mellitus. We have already stated that when an excessive amount of acid is present in the body, it is neutralized by the ammonia which would otherwise have been converted into urea (p. 327). For this reason the excretion of organic acids in diabetes is associated with a relatively increased elimination of ammonia and a relatively diminished excretion of urea in the urine. The source of the acetone and of the diacetic and beta-oxybutyric acids is of great theoretical and practical interest, for the resulting acidosis is apparently the most important cause of the dreaded diabetic coma (see p. 332). Unfortunately, however, the cause of the acidosis and the source of the acids is but little understood (see p. 328).

In diabetes, the nutrition of different parts of the body suffers in various ways. The crystalline lens of the eye may become opaque (diabetic cataract), and degeneration of the retina and choroid coat may develop. The arteries are often found to be sclerotic.

Tissues that are permeated with sugar seem to offer an excellent medium for the growth of micro-organisms, and it is well known how frequently diabetics become infected and how often these infections terminate in gangrene. The diabetic gangrene is due, in part, to the presence of excessive amounts of sugar in the tissue and, in part, to the diminished blood-supply caused by an associated arteriosclerosis. Patients with diabetes are furthermore very susceptible to tuberculosis, and here again the process shows a special tendency to develop into gangrene. Other complications, such as furunculosis, caries of the teeth, gingivitis and stomatitis, are also frequently present in diabetic patients.

We know comparatively little concerning the relation that lesions of the kidneys bear to diabetes mellitus. Albuminuria is a not infrequent complication of the disease.[55] In some cases it is due to a true nephritis, produced by the same cause which gave rise to the diabetes, such as arteriosclerosis, for example; in other cases it is apparently quite an accidental complication. When the albuminuria develops late in the diabetes, it may be questioned whether the continuous passage of sugar through the kidneys has not directly harmed the secreting cells. In this connection we may recall the glycogenic degeneration of the kidney so often found in diabetes.[56] The immediate cause of this degeneration, and its relation to albuminuria are, however, insufficiently understood. That primary lesions of the kidney may cause glycosuria (renal diabetes) seems very probable (see p. 346).

The amount of urine is often enormously increased in diabetes, and as much as ten or fifteen litres may be passed in twenty-four hours. This is undoubtedly dependent upon the abnormal quantity of sugar in the blood; for if, by proper methods, the latter be diminished, the amount of urine also diminishes. Conversely, the greatest diuresis occurs in the cases with the largest amounts of sugar in the urine. The accumulation of dextrose in the blood, or in certain tissues, seems to produce an intense thirst, and the water that is taken for this causes the increase in the amount of urine. Yet there exists no definite relation between the amount of urine, the excretion of sugar and the feeling of thirst; and it has been shown, for example, that even

though the same quantities of sugar are being excreted daily, the quantity of urine may be different in different patients.

Theory of Diabetes.—From the foregoing facts we shall now try to formulate a theory of diabetes mellitus. The sugar is excreted in the urine because of a hyperglycæmia—an excess of sugar in the blood. One cause of this excess in the blood is that the liver has lost the property of storing up the dextrose that comes to it either from the food (mild form) or from the splitting up of proteids in the body (severe form). To confirm the correctness of this distinction, however, further evidence is needed.

It is impossible to say to what extent the glycogenic functions of other organs, such as the muscles, are impaired in diabetes. It seems certain, however, that in some way the pancreas assists the liver and muscles in their glycogenic function, and that human diabetes is generally the result of a disturbance of the islands of Langerhans. The loss of the pancreas function not only seems to interfere with the power of the liver to store glycogen, but also to cause the liver to release its glycogen in amounts far in excess of those called for by the tissues. For, after the pancreas has been removed from dogs, even in the fasting state, hyperglycæmia and glycosuria appear at once, and the liver becomes glycogen-free much more rapidly than in starving dogs whose pancreas is intact.

In the milder cases of diabetes, it is possible that no other disturbances of function are present than the above-mentioned impairment of the glycogenic functions in the body. In the more severe forms of diabetes, however, there is undoubtedly a diminution in the ability of certain cells of the body, perhaps of the muscle-cells or even of all cells, to assimilate sugar. The pancreas seems to assist in the assimilation of sugar in the body, not only through its influence on the glycogenic function of the liver, but possibly also by furnishing an internal secretion that activates the glycolytic ferments in the muscles. This action of the pancreas is perhaps similar to that of the enterokinase of the intestines which converts a protrypsin into a trypsin, or to the intermediary body that plays such an important part in hæmolysis.

The glycogenic function of the liver may certainly be influenced

through the nervous system, as is proved by the effects of the experimental puncture of the fourth ventricle; and it is quite possible that the nervous system serves in some way to connect the liver and the muscles. This influence of the nervous system upon the glycogenic function of the liver would explain the etiological relation between nervous lesions and diabetes, a relationship that has been insisted upon by so many clinicians.

Finally, we know that a glycosuria may be caused by lesions of different organs, especially of the liver, the pancreas, the thyroid, the adrenals and possibly by diseases of still other organs. Ultimately, it may be possible to distinguish different forms of the disease according to their origin; even now, indeed, v. Noorden[57] has attempted such an etiological classification on the basis of the interrelationship of the ductless glands. And, even though diabetes is apparently associated in most cases with lesions of the islands of Langerhans, it is not improbable that these endosecretions may be influential in determining the characteristics of the particular case.

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CHAPTER VIII

THE METABOLISM OF THE PURIN BODIES. GOUT

The nitrogen derived from a certain class of proteids, the nucleo-proteids, is not excreted in the form of urea and ammonium salts to the same extent as is that derived from ordinary proteids.[1] The characteristic constituents that enter into the composition of the nucleo-proteids are the nucleinic acids. When these undergo cleavage, they give rise to the purin or alloxuric bases, among which are adenin, guanin, xanthin and hypoxanthin. A small portion of these bases appears in the urine as such, but the greater part is eliminated in an oxidized form, as uric acid. The uric acid and the purin bases are often spoken of together as the purin bodies.

The mechanism underlying the conversion of the nucleo-proteids into the purin bodies is one of ferment action.[2] From the nucleins of the cells a nuclease splits off the purin bases adenin and guanin. The latter are changed by a hydrolytic ferment into xanthin and hypoxanthin. An oxydase converts hypoxanthin into xanthin, and the latter in turn into uric acid. These ferments are widely distributed in the animal body. In man about fifty to sixty per cent. of the uric acid is destroyed by still another, uricolytic, ferment—uricase—chiefly in the liver, muscles and kidneys. As this uricolytic enzyme is absent from the blood,[3] a certain portion of the nitrogen of the purin bases appears in the urine as urea.

Most of the uric acid that appears in the urine is derived in this manner from nucleo-proteids that are broken down in the body, or from purin bases or related compounds, such as caffein or theobromin, that are taken in the food. Not all of the uric acid, however, is derived from these sources, for it is now practically certain that this acid may be formed synthetically in the human body, just as it is in the bodies of birds.[4] Nor does all of the nitrogen contained in the nucleinic acids appear in the urine as uric acid or related com-

pounds, for a certain proportion is converted into urea in the body. This latter fact gives some basis to the old conception that uric acid represents an early stage in the formation of urea.

The quantity of purin bases in the urine serves therefore as a rough index of the bodily consumption of nucleo-proteids and purin bodies, derived either from the cellular metabolism or directly from the food. Yet, as we have seen, it cannot serve as an accurate and absolute index of such consumption; for, on the one hand, not all of the nitrogen in the nucleinic acid appears in the urine as purin bodies, and, on the other hand, these bodies may be formed synthetically within the living organism.

Cell nuclei are very rich in nuclei-proteids; and when the food taken contains many nuclei, as is the case with thymus gland, for example, the amount of purin bodies in the urine is greatly increased. Conversely, if a person avoids those substances which can be readily converted into purin bodies, such as the nucleo-proteids of meats and seeds, the caffein of coffee, etc., the quantity of uric acid in the urine is diminished, and that which does appear there represents the amount actually formed within the body. The amount of this endogenous uric acid has been found to be different in different individuals, though it is fairly constant for the same individual at different times.[5] It is apparently somewhat influenced by the ingestion of large quantities of non-nitrogenous food.

The elimination of endogenous uric acid is increased whenever large numbers of cells rich in nucleo-proteids are being destroyed in the body. This was early demonstrated for a particular kind of cells, the leucocytes; and this fact, among others, led Horbaczewski to the belief that the leucocytes are a specific source of purin bodies, a view now proved to be incorrect.[6] Leucocytoses are, however, frequently accompanied by an increased elimination of purin bodies; and when this is so, we may assume that an abnormal destruction of leucocytes is taking place in the body. Very large amounts of uric acid are excreted in the majority of cases of leukæmia (64 per cent.). Gottlieb[7] has demonstrated in some leukæmias an increase in the excretion of the purin bases; while other observers,[8] in a series of cases, have found the excretion both of uric acid and of the bases to be increased. The leukæmic increase in

the purin bodies likewise speaks for an augmented destruction of leucocytes.

The urine of the new-born child also contains remarkably large quantities of uric acid. These are found at about the same time that uric acid infarcts are most liable to occur in the kidneys. The explanation of this increased elimination resides possibly in the marked destruction of leucocytes which occurs in the first days of life and which leads to a saturation of the tissues with the purin bodies, just as in leukæmia;[9] while the small amount of urine excreted at this time favors the precipitation of uric acid.

Gout.—Gout[10] is characterized by the deposition of monosodium urate crystals in various parts of the body, especially in the hyalin and fibrous cartilages, in the tendons, in the subcutaneous and intermuscular connective tissues and in the kidneys. These deposits take the form of clusters of needle-like crystals. No symptoms may be caused by such a deposition of urates, especially when it takes place gradually and in certain localities, as the subcutaneous tissues and some cartilages. These urate deposits, known as tophi, often attain a large size, and they may then break through the skin, or again disappear without having caused any unpleasant sensations. In these cases, it seems improbable that the uric acid should have been formed locally by the cells, for the strands of connective tissue are pushed aside, and the tophi increase in size by new deposits on their exteriors.

On the other hand, the deposition of urates in the tissues may lead to a more or less marked inflammatory reaction in the neighborhood, and this may be accompanied by the characteristic paroxysm of acute gout. Suddenly, or after some prodromal symptoms, the patient is awakened at night by violent pains in one or more joints, usually in the metatarsophalangeal joints of the great toes. The affected joint and the neighboring tissues become intensely inflamed, and the skin over them becomes œdematous. These very acute symptoms usually do not last long, and after a few hours or days they all disappear without necessarily leaving any alterations in the joint that can be demonstrated even by anatomical methods. These typical acute gouty paroxysms may recur at varying intervals; but gradually they become less and less characteristic, the patient becomes cachectic

and the "regular gout" is said to have become transformed into the asthenic form.

The exact cause of these typical paroxysms is uncertain. According to one view the inflammation is caused by the deposition of uric acid or some of its derivatives in the tissues. That this deposition is an important, if not the determining, factor in the gouty attack is indicated by the following facts: Before the paroxysm, the amount of uric acid in the blood is increased, whereas during the attack and shortly thereafter, the amount is greatly reduced. Again, it is possible to produce typical paroxysms in gouty individuals who have lived on purin-free food for a long time, by feeding them large amounts of food rich in the purin bodies.[11] Gouty attacks may occur, furthermore, following a pneumonia when nucleins (leucocytes) in large numbers are breaking down.[12] Finally, characteristic tophi have been produced in rabbits by injections of uric acid.[13] Following the injection the latter is converted into the insoluble sodium urate and about the precipitate are seen the inflammatory phenomena characteristic of the gouty attack, *viz.*, the infiltration of polynuclear leucocytes, the appearance of phagocytes and the growth of connective tissue. Indeed, it was demonstrated many years ago that the salts of uric acid have a far more rapid and irritating action than does uric acid itself. Apparently, therefore, it is the deposition of the crystallized urates which brings about the inflammatory reaction, which is not necessarily painful, however.

Why this deposition occurs periodically and only in certain tissues is not known. And we are equally ignorant concerning the nature of many associated gouty manifestations, such as the granular kidney and the heart changes, the pulmonary, nervous and ocular complications and the general cachexia.

It is said that a tendency to gout may be inherited, and that the disease may be caused by excesses in food and drink. We believe, however, that caution is necessary in the acceptance of these views, for they rest not upon convincing statistics, but rather upon so-called clinical experience and impressions. More accurate data on this subject are therefore very desirable. That chronic lead poisoning favors the development of gout can hardly be doubted,[14] though how it does

so is quite uncertain. The nature of the relationship between gout and diabetes mellitus, and between gout and obesity, are likewise unsolved.

Uric Acid in the Blood During Gout.—During, and also between, the gouty paroxysms, uric acid crystallizes out of the blood with abnormal ease, even though the diet has for months contained no purin bodies, and though the heart and kidneys are free from changes.[15] It crystallizes out of normal blood in a similar manner only when a large amount of nuclein compounds have been taken in the food. In pathological conditions other than gout, especially in leukæmia and in pneumonia after the crisis, however, large quantities of uric acid will at times crystallize out of the blood just as it does in acute gout. And in chronic nephritis with uræmia, uric acid may readily be demonstrated in the blood.[16] To explain the practically constant uric acid content of the blood in gout, one must assume that the power of certain organs to break up the acid has been diminished.[17]

The fundamental question as to the solubility of uric acid in the blood has recently been elaborated in its more important aspects by Gudzent.[18] As Emil Fischer first demonstrated, uric acid occurs in two forms, the one corresponding to the laktam formula, the other to the laktim formula. Both series form primary salts which differ only in their solubility. Gudzent was able to demonstrate that the laktamurate, while the more soluble, was extremely unstable and was immediately converted into the more stable laktim modification. He has shown further that radium is capable not only of retarding the change from the soluble to the insoluble salt, but also has the power to convert the insoluble laktim into the more soluble laktam.[19] Upon these observations is based the recently advocated and eminently successful radium therapy of gout.[20]

That uric acid exists in the blood only as the sodium salt appears well established;[21] accordingly, the view that it is combined with nucleinic acid in the blood and tissues seems untenable.[22] As soon as one hundred c.c. of blood serum contain more than 18.4 mg. of laktamurate or 8.3 laktimurate, the conditions are favorable for the deposition of the uric acid salts.[23]

More difficult of understanding are the causes of this supersaturation of the blood with uric acid and of its deposition only

in certain tissues. Significant with respect to the latter is the observation that cartilage possesses an especial affinity for uric acid, which crystallizes out as sodium urate in this tissue. We are thus brought a step nearer to an understanding of how tophi are formed.

Another question still undetermined is whether, with a given concentration of uric acid in the blood, deposition occurs more readily in gouty individuals than in non-gouty. Leukæmia is a condition in point; here, though unusually high uric acid values are observed, gouty manifestations are distinctly infrequent. Nevertheless, they are occasionally observed in typical form.[24]

The Uric Acid in the Urine in Gout.—Previous to the gouty paroxysms, there is a diminished excretion of uric acid in the urine; whereas, during and just after the paroxysm, more is excreted not only than before,[25] but also than in the intervals between the attacks, and this too on a meat-free diet.[26] The excretion of the purin bases is also said to be increased along with the increase in uric acid, though there is some doubt as to this. The endogenous uric acid excretion exhibits a similar behavior; after the paroxysm, indeed, it may fall below the normal[27] and in the intervals it remains at the lower limit of the normal.[28] If food rich in nuclein compounds, *e.g.*, thymus, be taken during the paroxysm, the uric acid is not excreted so well as it is by a normal individual.[29]

In chronic gout, and during the intervals between the paroxysms of acute gout, no definite abnormalities in the excretion of uric acid can be demonstrated, although Soetbeer believes that after the administration of meat the excretion of uric acid does not follow precisely the normal course, and that in some cases it is quantitatively diminished or delayed.

Brugsch and Schittenhelm[30] found that the excretion of endogenous uric acid was, on the average, diminished, even though the amount of uric acid in the blood was increased and the kidneys were functionating properly. The formation of urea from exogenous purin bodies was delayed in gouty individuals; while the total uric acid formation from all sources was likewise retarded. Hence, there exists a disturbance of uric acid formation, uric acid destruction and uric acid elimination. Bloch[31] has made similar observations and emphasizes the importance of the disturbance in endogenous purin

metabolism. Umber,[32] on the contrary, whose curves indicate a subnormal elimination of uric acid in the gouty, regards the retention of uric acid as the essential feature. That retention does play an important part seems to be indicated by the success generally reported from the use of atophan[33] which apparently exerts a specific eliminative action on the kidneys.

One might be inclined, therefore, to attribute the increase of uric acid in gouty blood to an insufficient excretion of urates by the kidneys, a supposition which receives some support from the fact that other nitrogenous waste products may also be retained in the body, both in the acute paroxysms and in chronic gout.[34] Indeed, evidence has been accumulated which indicates that the kidneys are functionally deranged even early in the course of gout.[35] The gouty granular kidney, however, is a late manifestation. That unusual conditions are present would appear from the retention of ammonium and potassium salts during the gouty paroxysm.[36] The metabolism of proteids, other than that of the nucleo-proteids, is entirely normal in gout.[37]

The Cause of the Local Deposits of Urates.—According to many of the best observers,[38] the local deposits of the urates in gout are caused by changes in the cells of the affected regions. This seems to be true in the primary attacks at least. As has been mentioned, however, there is less reason to believe that the more chronic deposits in the subcutaneous tissues, etc., are caused by primary cellular changes. Ebstein has laid great weight upon a primary necrosis of the tissue as the cause of the precipitation of urates, but later researches have not supported his views. The solution of this problem would seem to reside in studies which shall determine in what way, and to what degree, substances related to uric acid are held in solution.

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CHAPTER IX

CONSTITUTIONAL DISEASES AND DIATHESES

THUS far, we have considered metabolic anomalies in so far as they have concerned variations in the amounts of materials utilized by the body, or alterations in the catabolism of the normal constituents of the food and tissues. The index of such anomalies is the appearance of incompletely metabolized substances in the urine—findings which open to us the significant, extensive and practically unexplored domain of the so-called intermediary metabolism.

It has already been noted that in the normal metabolism of certain organs, there arise substances which influence the activity of other organs. Thus the field of intermediary metabolism coincides with that of the chemical correlation of the organs,[1] which seems to explain from the physiological and pathological points of view what investigators have long since sought to establish from the morphological, *viz.*, the indivisibility of the organism. The nervous system has until recently been regarded as the essential mechanism whereby the functions of the different bodily units are harmonized; now, however, the belief is held that many other organs, perhaps all, mutually influence one another in a chemical way by means of the so-called hormones. The sphere of the latter is apparently unlimited, for the activity even of the nervous system may be stimulated or depressed to a great extent by chemical means. The subject is so vast and complicated, however, that we can touch upon only a few features which seem perhaps best established.

The gonads, the hypophysis, the pineal gland, the thyroid and the suprarenals, in some complex and unexplained manner, are not only mutually interdependent in their own development, but they influence also the growth of the bones, the skin, the muscles and the general bodily and mental structure. The bone changes occurring in pregnancy and after castration have long been familiar to us; while osteomalacia has been ascribed to a disturbed ovarian function.

Disease of the hypophysis (see pp. 318, 348, 415) plays a part in the causation of acromegaly, a condition characterized by

a hyperplasia of the bones and soft tissues at certain points, associated with inflammatory manifestations; further, by marked deposits of fat beneath the skin, and by a diminution of both mental and physical, particularly sexual, power. In all probability these disturbances are the result of an increased functional activity of the cells of the anterior lobe of the hypophysis. Speaking for this are the benefits observed following removal of the gland in cases of acromegaly.[2] That the hypophysis and the sexual glands are intimately related would appear also from the specific changes which the hypophysial cells undergo in pregnancy.[3] The thyroid and the hypophysis are also closely correlated; the former is often affected in cases of acromegaly, and, furthermore, myxœdema and acromegaly have certain symptoms in common.

All of this goes to show that caution is indicated in attributing to a particular organ the primary changes leading to acromegaly; indeed, it is especially characteristic of all of these "nutritional disorders" that they exhibit manifestations which might be due to a lesion of any of a number of organs coincidently involved, thus rendering the determination of the primary disturbance practically impossible.

In **pineal gland disease,**[4] the characteristic clinical picture is in many respects the antithesis of the acromegalic, in that we observe premature development of the bones, skin, hair and sexual organs, and often a mental precocity. As for the **thymus,** its entire anatomical development, its persistence through adolescence, its regression as growth nears completion—all speak for its rôle in the building of the body. The condition known as persistent thymus has a clinical bearing. The so-called status thymico-lymphaticus[5] rests in part upon a constitutional, and, in part, upon a morbid basis. I am not prepared to say, however, in what way the thymus is concerned in this condition; it is possible that the gland affects the sexual organs and the nutrition of the bones. In the cases of sudden death among children, however, the rôle of the thymus cannot be overlooked.

In the foregoing conditions, the disturbance in function of one organ carries with it a disturbance of one or several other organs. What conclusion can we draw from this as to the effect of such

changes upon the organism as a whole? This opens up the problems of "local pathology" as contrasted with "constitutional pathology." Formerly, emphasis was laid upon the involvement of the entire body in most diseases;[6] as evidence of this were the constitutional and crasial teachings. Later, under the influence of pathological anatomy and physiology, interest turned to the disturbances in structure, or in function, of certain organs and organ-systems. The physicians of our generation have acquired their training in this strongly localistic atmosphere, in which everything was explained on a physical or chemical basis and was interpreted in terms of weights and measures. We regarded scornfully the crases and diatheses of the earlier teachers, and forgot how narrow we ourselves were becoming.

Now the pendulum has swung back once more, and we are beginning to understand that this "local pathology" is not comprehensive enough. Thus we meet with disturbances of function for which no organic substratum can be discovered—or indeed could be responsible—and in which a more general and extensive derangement must be assumed; while in some conditions, though a local change is found, and is without doubt etiologically significant, such a change is not sufficient to explain the functional disturbance in all of its phases.

This does not mean, however, that the older teachings must be readopted *in toto,* but only that certain fundamental truths which they contained must be employed in building a new conception of pathology. Indeed, we must pick to pieces and analyze the elements of the diatheses, the dyscrasias and the constitutional anomalies—the scrofulous, the hæmorrhagic, the gouty and the arthritic diatheses—and determine what of truth they contain. The older conception of the diatheses has again gained a foothold among the pediatricians in Germany, at least. We refer, in particular, to the lymphatic status and the exudative diathesis.[7]

Let us cite a few examples of constitutional diseases and peculiarities. The serum-albumins of different species are for the present chemically indistinguishable, yet each is shown to have individual characteristics by the phenomena of precipitation. A given serum-albumin will not, as a rule, destroy the erythrocytes of animals of its own species. In cases in which

hæmolysis does occur, we may assume that there exists a constitutional anomaly of the animal affected. Even though this peculiarity has been demonstrated only for a single type of proteid and for a single type of cell, it is likely that there exists a general constitutional fault. Again, in hæmophilic families, the blood coagulates slowly. There is a deficiency in thrombokinase,[8] present in all the tissues normally. This deficiency involves the blood-corpuscles, so far as our present knowledge goes, yet it is probable that all the other cells are likewise poorly supplied with this ferment.

Further, taking tuberculosis as an example of the infectious diseases, we have reasons to believe that in this condition the body as a whole is affected. Tuberculosis and syphilis were regarded as general diseases long before their infectious nature was determined; thus the term syphilitic diathesis was once employed. Later, when our interests centred in anatomical and bacteriological studies, tuberculosis in particular was regarded from the localistic point of view. Still later came the proof that in many infections—in typhoid fever, for example—the causative organisms did not remain localized, but entered the blood and caused changes in the most widely separated organs; and that in cases of pulmonary tuberculosis the bacilli might also invade the blood and the organs.[9] The general nature of the tuberculous infection was further confirmed by the discovery of v. Pirquet[10] which pointed to a cutaneous change in consequence of a general infection. The most significant feature of the reaction is its appearance even when the disease focus is insignificant and causes no symptoms. Could we establish a similar reaction on the part of other tissues, we should be fully justified in calling tuberculosis a constitutional disease.

In syphilis the principles involved are much like those in tuberculosis. As pointed out by Martius the conception of a constitutional syphilis arose by way of contrast with the localized primary lesion; yet the appearance in other parts of the body of specific luetic manifestations does not say that the entire organism is involved. Conditions such as tabes dorsalis, on the contrary, which are not immediately syphilitic, may well be regarded as due to a constitutional alteration of the cells on a luetic basis. The principles underlying the luetin and Wasser-

mann reactions are also in keeping with the conception of a constitutional disease.

The question arises as to the features which distinguish such a general pathological alteration from disease in the current application of the term. The mere fact that in the former a number, perhaps all, of the organs are involved is too unstable a criterion, fluctuating as it does from time to time with the development of our knowledge. We are constantly discovering indeed that diseases to all appearances local are in reality affections of the most extensive type. The infections are a case in point. In the mere matter of a widespread involvement, therefore, many, or perhaps all, diseases are general in that they usually produce changes in more than one organ; while the subdivision into acute and chronic forms would be as applicable to constitutional disorders as to the infectious diseases, for example.

But features of another kind characterized the constitutional diseases, the dyscrasias and the diatheses as the terms were employed by the older writers.. First of all, was the fact that the manifestations were permanent. Though the process might at times begin abruptly, it lasted for years and even throughout life. Frequently, furthermore, there was a congenital element. Hæmophilia is illustrative of these factors. As is well known, this condition is inherited in certain families, being transmitted through the females, who themselves are unaffected, to the males.

Still another characteristic of the constitutional diseases is their resemblance in a way to malformations or to anomalies of structure[11] rather than to diseases in the present acceptance of the term. The hæmophiliac is, as a rule, not sick so long as there is no provocation for bleeding; rather is he endowed with a tendency to become sick. In the same sense, I interpret the exudative diathesis of Czerny.

Some of the conditions under discussion, however, are more than a mere disease tendency; they are actually diseases. Thus the so-called uratic diathesis is frequently associated with manifestations due to renal sand and renal stones. It is convenient to define diathesis as a tendency to disease, and a constitutional disorder as a condition embracing a disease. At

any rate, the attempt should be made to distinguish between disposition and diathesis, on the one hand, and actual disease, on the other.

Three possible factors are concerned in the etiology of the constitutional anomalies. A portion of them are congenital in the sense that the germinal cells have been injured. It is not difficult to understand how an injury to these cells may lead to widespread cellular abnormalities in extra-uterine life. The anomaly may then be the direct outcome of this early cell injury; or it may be expressed in a weaker *anlage* which later leads to disease because the possessor is unable to resist the wear and tear of every-day life. This is well illustrated in the inherited psychopathic tendency of certain individuals.

In other cases the condition is acquired. The causative factors in this type are infections, intoxications and faulty living conditions in the way of light, air, habitation, sleep and food. It is well known that these latter factors tend to diminish the individual's resistance, his efficiency, etc. Under their influence an inferior strain of men is produced. The action is not merely quantitative, *i.e.*, leading to a physical and mental subnormality, but also qualitative, as the unequal resistance to infections indicates.

In the older descriptions of the diatheses and constitutional anomalies, no distinction was made between those of infectious origin, on the one hand, and the toxic and congenital forms on the other. To-day the infectious diseases are sharply separated from the latter. Yet it is just in the infections that our recently acquired knowledge of the functional and morphological changes in the different organs have given us an insight into the widespread nature of bacterial processes. The conditions of general weakness so often seen after the infection has subsided have much in common with what we are pleased to call constitutional disorders. This is particularly true of such chronic infections as malaria, syphilis and tuberculosis, which indeed were formerly classified as dyscrasias, diatheses and constitutional diseases. We repeat, therefore, that in the consideration of the infectious diseases, we encounter at one point or another the various elements which go to make up a constitutional disorder—at one time direct mani-

festations of the infection, at others a pronounced depression of the general nutrition, functional disorders of the organs, and the tendency to peculiar complications, as, for example, tabes and paralytic dementia in syphilis.

As for the chronic intoxications and the cachectic states observed in malignant processes, we are of the opinion that they properly belong in the category of constitutional anomalies. This indeed was the old view; while now the general tendency is to assign them elsewhere. That chronic lead poisoning is a constitutional disorder is evidenced by the impaired nutrition, the involvement of many organs (brain, nerves, vessels and kidneys) and the tendency to other diseases, such as gout. By cachexia is meant not a mere undernourishment, but rather a nutritional state which in general is below par. Still to be solved in this question is the cause of the characteristic cachectic color of the skin, and of the œdema of the tissues, both of which indicate the general nature of the process.

The literature devoted to constitutional diseases and diatheses speaks for the great diversity of the conditions included therein. This is due in part to the great difficulty in distinguishing between diseases which are local and those which are general, and in part also to the tendency to place among the constitutional disorders those conditions which have no distinct local pathology. Diabetes mellitus and diabetes insipidus are illustrative of this. Depending upon the point of view, the flooding of the tissues with sugar may be regarded either as secondary to some local lesion, or as proof *per se* of the constitutional nature of the process.

Obesity is to be regarded as a constitutional disease only in those cases in which there is actually a metabolic anomaly present, not when the condition is due to excesses in eating. Gout we have seen results from a disturbance in the metabolism of the purin bodies. Whether this is indicative of a constitutional process depends, to a great extent, upon individual opinion, just as in the case of diabetes, though not unimportant is the question as to what cells are involved in the disturbance of purin metabolism and how widespread is the disorder.

As proof of the constitutional nature of gout and of diabetes, has been urged the close relationship between the two, as well

as to obesity. It is true that these three conditions frequently show a family tendency and that in individuals with any one of the three disorders there is often a family history of the other two. Yet these observations scarcely afford a sufficient basis for the assumption of a constitutional anomaly. And in particular is there need for a greater accuracy in the diagnosis of gout, and for a better understanding of the relationship of obesity to nutrition. These are essentially physiological problems, entailing a fuller knowledge of the metabolism of the purin bodies and of sugar. And finally, there remains the problem of the position of diabetes, obesity and gout—particularly the latter—in the calculous, uratic and arthritic diatheses.

A more extensive clinical knowledge, in my opinion, is what is necessary to a better understanding of the constitutional diseases and diatheses. There has been too little empiricism in the past and too much preconception; too much mere assertion and too few observations as to the fundamental manifestations and attributes of the diatheses. This indefiniteness is particularly true of the so-called arthritic diathesis, under which in the literature are included absolutely unrelated conditions.

The exudative diathesis and lymphatism are apparently closely related, and both are in turn related to the arthritic constitution. Lymphatism and the exudative diathesis, as they are seen in the child, have what most of the other reputed constitutional anomalies have not, *viz.*, a well-elaborated dispositional and clinical basis. The exudative diatheses of eosinophilic nature (asthmatic catarrh, mucous colitis) are especially interesting. Spasmophilia of children, characterized as it is by an augmented nervous irritability on the one hand, and on the other by a relationship to tetany and the later development of nervous disorders, urgently demands further study.

The uratic diathesis carries with it all the inherent interpretative difficulties that have been noted in connection with gout. On the other hand, it is characterized by a tendency to cause direct manifestations. As for rickets and chlorosis, we may speak only of general diseases, not of diatheses, otherwise we should lose sight of the actual significance of a

constitutional disorder, and include under the latter any local disease with involvement of other organs.[12]

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[10] Die Allergie; also Ergeb. d. inn. Med., 1908, i, 420.
[11] J. Cohnheim: Allg. Path., ii, 1st edit. (Introduction); Krehl, Path. Physiologie, 6th edit. (Introduction).
[12] For more recent literature see His, Pfaundler, Block, Mendelssohn: Kongr. f. inn. Med. 1911 (lit.); Mors, Lubarsch-Ostertag, 1910, xiv.

CHAPTER X

FEVER

FEVER is characterized by a pathological increase in the temperature of the body. Whereas the rectal temperature of a healthy individual at complete rest rarely exceeds 37.5° C. (99.3° F.), it may, in febrile states, reach 41° or 42°, and very exceptionally, even 44°.

As a rule, the diurnal variations of fever are of the same character as are those which take place in health, *i.e.*, there is an elevation toward evening and a fall toward morning. Those who work at night and sleep during the day show at times the inverse type of diurnal variation both in health and fever. Thus we see that the same causes, such as food, light, work, etc., which influence the temperature curve of healthy persons, affect also the variations in the temperature of febrile patients. Nevertheless, the temperature in fever is much less constant than in health, and the considerable variations that it undergoes are due partly to external influences and partly to causes which escape our present methods of observation.

Variations in the Clinical Picture of Fever.—These depend, in the first place, upon the cause of the fever. Most fevers are of bacterial origin, and, as is well known, bacteria may vary in their virulence, conditions of growth and duration of life—all of which determine the temperature-picture of the disease which they cause, as well as its other manifestations. So far as malarial fever is concerned, we know that the paroxysms occur when the causative organisms are at a particular stage of development. The same is true of certain septic diseases. All in all, therefore, despite certain deviations, we may say that the infectious diseases as a rule have characteristic fever curves.

In the second place, the clinical picture presented by fever depends largely upon the condition of the individual affected—upon his strength, nutrition and degree of immunity. During epidemics, different febrile manifestations occur in different individuals. We may say, in general, that young and strong patients react with a higher fever to an infection than do old and feeble ones. Indeed, the temperature may

actually fall in the latter class of patients. We possess analogous experimental observations;[1] thus, it is impossible to produce fever by the injection of certain non-bacterial chemicals into fasting animals, though the same substances will regularly cause a fever in well-fed animals. Bacterial infections, on the contrary, may cause an elevation of temperature whether the animal be starving or well fed.

The numerous other symptoms seen in fever—some due to the fever itself, others to its underlying cause—are also subject to considerable variations. These depend in part upon the height of the temperature, for this influences the rate of the proteid and other decompositions, as well as the cardiac and respiratory rates. Yet no exact ratio exists between the severity of these phenomena and the degree of temperature, because other factors, especially toxic influences, play so great a rôle. This has already been discussed so far as the pulse-rate is concerned (see p. 55).

Indeed, we may say, in general, that the symptoms of infection and intoxication predominate in the clinical picture of fever, and that many of the phenomena which were formally attributed to the high temperature are now ascribed to the action of toxins. Thus the psychic changes, the gastro-intestinal disturbances and the susceptibility of the respiratory tract to complicating inflammations, are all of toxic rather than of thermic origin. They are rarely seen in the "aseptic fever" following simple fractures; whereas, they are most prominent in such pronounced intoxications as typhoid fever. These symptoms also depend to a certain extent upon individual peculiarities—heavy drinkers, for example, being very prone to show serious nervous manifestations.

These various considerations go to show how difficult it is to distinguish between the clinical picture of fever *per se* and the manifestations dependent upon the cause of the fever. Indeed, they often merge so closely into one another as to be incapable of separation. A more intimate knowledge of the characteristics of the etiologic factors, particularly those of the infectious diseases, will probably tend to do away with the present tendency of regarding the febrile picture as a well-demarcated unit in the disease process as a whole.

The Causes of Fever.—The most diverse causes may give rise to fever.[2] It may be produced, first of all, by the en-

trance of living or dead bacteria, or their products, actually into the blood. Yet the mere presence of micro-organisms in the circulation does not necessarily raise the temperature of the body, for many bacteria which produce fever in certain animals fail to do so in others. Indeed, an animal may die from an infection and its heat production may be markedly increased, and yet, on account of the elimination of the extra heat from the body, there may be no rise of temperature.[3] This would indicate that the fever in bacterial disease is due to the disturbance of some definite mechanism. Protozoa may also give rise to fever, as in the case of malaria and of certain experimental infections.[4]

The substances that cause the fever are very possibly of a proteid nature, for complex substances isolated from the bodies of bacteria may give rise to fever if injected into men or animals.[5] It is questionable, however, whether these substances are themselves proteids, or whether it is merely difficult to separate them from proteids. Some have attempted to show that there is a non-proteid, fever-producing substance common to all bacteria,[6] but the evidence for this is very inconclusive.

Though bacteria and bacterial products are, undoubtedly, the most important causes of fever, they are not the only ones. Fever may be produced by the destruction of large numbers of cells in the body, even though micro-organisms play no part in the destructive processes. As examples of such, we may recall the fever that so frequently follows a simple fracture, or that which may follow large interstitial hemorrhages.[7] The substance which gives rise to these aseptic fevers is still unknown.

The fact that fever may be produced by bodies not derived from bacteria has led to careful studies concerning the action of numerous chemical substances upon the temperature of warm-blooded animals. These studies[8] have demonstrated that fever may be caused by the injection of various forms of proteids, whether the latter are assimilated or not, and whether they be of complex or comparatively simple structure. Elevations of temperature also follow the injections of many organic compounds and salts. Different animals, furthermore, differ in their susceptibility to the action of these substances.

It has long been known that injections of certain

salts may produce fever in animals. Finkelstein has recently made the interesting observation that the oral administration to infants of a one to three per cent. solution of sodium chlorid likewise causes an elevation of temperature. In infants suffering from gastro-intestinal conditions, smaller amounts, or weaker concentrations, of such solutions, are necessary to bring this about than is the case with healthy infants.[9] In adults, the parenteral introduction of isotonic salt solution causes fever. But individual differences in susceptibility are especially marked in the tendency to exhibit this so-called sodium chlorid fever. (Recent work[10] has questioned the authenticity of the febrile reactions following salt injections, attributing the fever rather to impurities in the water used to dissolve the salt. Certain by-effects of salvarsan have been laid to the same cause. The use of water freshly distilled obviates this factor.—Ed.)

Is it not possible that a single chemical substance is the cause of all fevers? Though this is conceivable, our present information[11] does not enable us to identify it. I am of the opinion, however, that such an hypothesis is almost necessary in view of the fact that a single mechanism seems to underlie all fevers. Common to all infections is a marked cellular destruction from which this hypothetical substance might be assumed to arise. The many studies devoted to this problem have shown, among other things, that the destruction of red blood-cells,[12] whether they be those of the particular animal itself, or from animals of the same or different species, gives rise to fever-producing substances which pass into the serum and do not primarily cling to the red cells.

The blood-platelets are also of undoubted influence in the causation of fever.[13] The injection of intact platelets (obtained in citrate solution) causes no febrile reaction; but as soon as they are disintegrated, they give rise to substances of a pyrogenic character. (Vaughan[14] and others have shown that typical fevers may be produced by the enzymic destruction of proteids in the body; and Mandel[15] has stated that fever may be produced by the administration of purin bases, such as xanthin or caffein.—Ed.)

The Relation of the Nervous System to Fever.—Granting that fever may be produced by the action of micro-organisms and

of chemical substances, bacterial or otherwise, the question arises as to whether these are the only causes of fever. That the nervous system exerts an important influence upon the heat regulating centre, is well known. Thus, a division of the cervical cord in animals brings about a marked disturbance of the heat-regulatory apparatus. Different animals behave differently in this respect, depending upon the level of the injury. Rabbits with a severed dorsal cord react as do healthy animals,[16] if the heat loss due to vasomotor paralysis is held within bounds by an elevation of the external temperature to about 22° C. The chemical heat regulation of such animals is preserved, for they react with fever to infections and to the injection of pyrogenic substances. If, however, the division be made above the first dorsal segment, the animals lose both their physical and chemical regulation; in this case a surrounding temperature of about 29° C. is necessary to maintain their body temperature at its normal level, while their power to react with fever is entirely gone.

The probabilities are that when the cord is severed in the cervical region, the cervical and dorsal sympathetic fibres are cut off from the central nervous system; for a division of the dorsal cord, plus a resection of the stellate ganglion, or a severance of the seventh and eighth cervical roots—whence the sympathetic originates to pass to the stellate ganglion—produces the same results. The fact that injections of epinephrin and cocain likewise cause fever[17] is in keeping with the assumption that the sympathetic system plays an extremely important part in the process; and we shall encounter another proof of this in the behavior of the blood sugar in fever. Rumpf has shown that narcosis in cool external temperatures leads to a considerable diminution in heat production, guinea-pigs exhibiting a fall of 10° C., and more, under these conditions. An intact nervous apparatus is essential also to the production of fever, the latter not appearing, as we have seen, after section of the cord high up, or when an animal is narcotized.

In view of the importance of the nervous system in the production and regulation of fever, there is no reason to believe that the heat-regulating centre may not be primarily diseased or influenced by impulses from other parts of the central nervous system. Many observations purporting to be examples of such a nervous fever will not stand the

scrutiny of a rigid criticism. For example, in poliomyelitis, polioencephalitis and meningitis, the elevation of temperature is probably due to the infection; while in other conditions, such as large cerebral hemorrhages, it is due in all likelihood to the absorption of the disintegration products of the red corpuscles or the injured tissue cells.

In other conditions, the nervous lesion seems to exert a more direct influence upon the bodily temperature. At times, general convulsions, associated with stupor, lead to excessive elevations of temperature, though at other times, when the convulsions are produced by certain drugs, there may be an actual reduction of temperature.[18] In the latter instances, the heat regulation is affected, and it would seem that the poisons leading to the convulsions also diminish the production of heat in the body.

We know that muscular movements will raise the temperature of even a healthy person, if the elimination of heat is interfered with—an observation that has also been experimentally established in animals.[19] If, however, the extra heat that is liberated during exercise can be eliminated, no rise of temperature results. As a rule, therefore, convulsions do not materially alter the body temperature. A rise of temperature is especially apt to be produced by convulsions when there is reason to believe that the heat-regulating mechanism is paralyzed. For example, fever is rarely present in the earlier stages of tetanus; and the rise of temperature toward the end of the disease would appear to be caused by a paralysis of the heat-regulating centre. The high temperature that has been observed in many cases of status epilepticus and in heat-stroke is perhaps to be explained in a similar manner. Possibly, also, the elevations of temperature in hysterical individuals, which have been described by some writers, are of this character, though never having witnessed a true hysterical fever, I personally feel somewhat skeptical as to its existence.

Experimentally, it is possible to produce fever in animals by injuring the brain. A characteristic example of this is the temperature elevation which can be caused in almost every case if a long needle be thrust into the mid-brain of rabbits.[20] The fever produced by such a puncture begins several hours after the operation, continues for days and may reach a considerable height. The production of heat in the body

is increased, and the loss of heat likewise, but to a lesser degree. The loss of heat by evaporation from the skin is relatively greater than it is in the case of infectious fevers. Furthermore, the increased heat production is almost entirely due to the (augmented) consumption of non-nitrogenous material, a fact which also serves to differentiate this from ordinary fever, in which a characteristic hydrolytic cleavage of proteids takes place.[21] During the fever resulting from a puncture of the brain, the liver[22] is the warmest organ of the body, and its glycogen store rapidly disappears. Indeed, unless there is a store of glycogen in the body, no rise in temperature follows the puncture of the brain. It is apparent, therefore, that the elevation of temperature caused by puncture of the brain differs from that due to an infection in several important particulars.

Experimental lesions of other portions of the brain, *i.e.*, other than the typical mid-brain puncture, may also produce fever, according to certain observers,[23] though with a far less degree of certainty. The problems concerned here open a wide field for research.

It is very questionable whether fever is ever caused by reflexes. The elevations of temperature which may occur during biliary colic and those which may follow urethral operations (catheter fever) are often regarded as instances of reflex fevers. Yet, in my opinion, it is much more probable that we are here dealing with fevers caused either by the absorption of toxic products or by actual infections.

Elevations of temperature have been observed after injuries to the spinal cord. Such elevations occur most frequently in association with severe contusions of the cervical region, produced by fractures of the corresponding vertebræ. Temperatures as high as 42° to 44° C. (106.5° to 111° F.) have been observed in such conditions.[24] It is possible to produce the same effect experimentally by crushing the uppermost part of the cervical cord of large dogs. After injuries of this kind, the temperature does not always become elevated, and it may, indeed, fall. These varying results of the experiment are due to the fact that if the cord of a warm-blooded animal be severed high up, the body temperature becomes a plaything of

circumstances. When the temperature of its surroundings is high, the heat production is increased, and when the surrounding temperature is low, the heat production is diminished; in other words, there is no regulation of the production of heat in the body. This is one reason why animals easily become overheated or cooled off after they have sustained severe contusions of the cervical cord.

Other factors besides the surrounding temperature also play a part in the elevation of the temperature that takes place in cord injuries, though upon these points we are less certain. It is possible, for example, that the peripheral circulation is so altered that the loss of heat from the body is diminished. Furthermore, the crushing of the cord—a manner of injury which seems to be an important requisite for a high temperature—may possibly produce an irritation of the corresponding muscles, and so directly increase the production of heat in the body. This is apparently the reason why the elevation of temperature is more likely to take place in men and large dogs than it is in small animals. The former have a relatively small surface from which to lose heat, and a relatively large musculature in which an increased heat production can take place. We see, therefore, that the rise of temperature that may follow cord injuries is due, partly, to a loss of heat regulation, and partly, in all probability, to an increased production and a diminished loss of heat from the body. The condition, therefore, differs essentially from that present in true fever (see p. 391 *et seq.*).

The Normal Regulation of the Body Temperature.—The temperature of man is maintained at an almost constant level under the most varying conditions; indeed, it varies less than that of any other animal. We shall, therefore, first consider the mechanism by which the temperature is normally maintained at this uniform level.[25]

If large quantities of heat are suddenly set free in the body from any cause, such as muscular work or the ingestion of large amounts of food, the total loss of heat from the body is correspondingly increased. The cutaneous vessels dilate and the warmer skin loses heat more rapidly by radiation and conduction. The affected person perspires more freely,

and the loss of heat by evaporation of water from the lungs is likewise increased. Whether the one or the other of these various means for eliminating heat is utilized to a greater or less extent in the individual case depends upon a variety of conditions, which cannot be considered in this place.

If, on the other hand, a warm-blooded animal is exposed to cold, it is able to protect itself from considerable losses of heat, which would otherwise tend to reduce its temperature. The skin vessels contract and the heat losses through conduction and radiation are diminished. Men ordinarily wear thicker clothes under these circumstances and so surround their bodies with a layer of comparatively warm air. The fur of animals and the fat of obese persons also diminish heat losses. By these means it is possible to maintain the normal bodily temperature, even when the individual is exposed to moderate degrees of cold. If, however, this mechanism is insufficient to meet the emergency, then a new factor is called into play. The production of heat in the body is increased, the site of this increased production being the muscles, according to the best authorities.

When a man is exposed to cold, therefore, the first regulatory mechanism that serves to maintain his body temperature at the normal level is of a physical character, *i.e.*, losses of heat are prevented. As we have just seen, however, this means of regulation may be insufficient, and the exposure to cold is then followed by an increased production of heat in the body. Frequently, the individual feels chilly and shivers, and thereby increases the combustion in his body; but, even though no gross muscular movements occur, the body metabolism may be increased, as has been proved by recent experiments. In either case, the extra heat is generated mainly by the combustion of non-nitrogenous material,[26] just as it is when heat originates from muscular activity. This regulation of the body temperature by variations in the heat production is termed a chemical regulation in contradistinction to that which depends upon variations in the heat losses, the so-called physical regulation.

The point at which the chemical mechanism steps in to maintain the temperature of the body depends in part upon the degree to which the animal is able to limit his loss of heat, and in part upon the amount of exercise and food which have been taken. The heat that is immediately set free after exercise or eating is

ordinarily quickly disposed of by an increased elimination of heat; but if the body is exposed to cold, this extra heat serves to maintain the body temperature. It thus obviates the necessity of calling the chemical regulation into play.

These are, in brief, the means whereby the healthy man regulates his bodily temperature under varying external and internal conditions. Under certain circumstances, however, even the normal mechanism is insufficient to keep the body at a constant temperature. For example, if heat be applied to the surface of the body, and if, at the same time, the compensatory loss of heat be interfered with, a rise in temperature necessarily follows. For this reason, every man becomes warmer in a steam bath, or in a warm-water bath of 40° C. (104° F.) or over. Possibly, however, some become warmer than others under the same conditions.

An increased production of heat within the body by excessive chemical decompositions may also cause a rise in temperature, an event of more frequent occurrence than is generally supposed.[27] Muscular exertion, even if not very severe, may thus raise the temperature of the body. In this respect, different individuals certainly react differently; the novice becomes overheated in doing a certain piece of work more easily than does the adept, mainly because he uses more energy to accomplish the same result. Another factor that is of great importance here is the ease with which heat may be eliminated from the body. This explains many of the apparent contradictions met with in the literature concerning the effect of muscular exertion upon the body temperature. The man that makes the ascent of Monte Rosa does not become warmer from the great exertion, because the low temperature and the dryness of the surrounding air greatly favor the loss of heat from his skin and lungs. Yet more recent investigations have shown that severe muscular exertion performed in high altitudes at low temperatures often causes fever.[28] On the other hand, the temperatures of soldiers frequently rise during forced marches, for they are heavily dressed and they must often travel in a warm, moist climate.

Heat-Stroke.—If the temperature of the body becomes considerably elevated from such outside causes, we speak of it as heat-stroke.[29] The temperature under these conditions may

reach 43° C. (110° F.) or over, the pulse becomes rapid, the patient becomes dizzy or delirious, and in severe cases, coma and death terminate the scene. The high temperature often persists in these patients for hours, or even days, after the actual cause of the stroke is over. This would seem to point to some injury to the heat-regulatory mechanism. Heat-stroke patients are often described as being pale, livid or cyanotic, conditions which indicate an improper peripheral circulation and a consequent imperfect regulation of the heat losses from the surface of the body. This poor peripheral circulation is apparently due to an injury to the regulating centres in the brain, though the nature of this injury is not known.

The experience of military surgeons has taught us that excessive heat is most liable to affect those who are in some way indisposed, who are foot-sore or who are convalescent from severe illness; and it has frequently been observed clinically that persons who are ill, particularly anæmic or tuberculous patients, are especially prone to show a rise of temperature after exercise, or even after meals.

In heat-stroke, the conditions are very complicated, and the rise of temperature is not due to external forces alone. Other factors are certainly present, for different individuals show considerable differences in their susceptibility to changes in their environment. Some lose heat more readily than others, a fact that is especially true of thin individuals as compared with stout ones. Heart lesions render a patient very susceptible to heat-stroke, for a good peripheral circulation is a necessity when the losses of the heat from the body must be increased.[30] (An overindulgence in alcohol also renders an individual more susceptible to heat-stroke. Finally, those who have once had a sunstroke may manifest for years a markedly increased susceptibility to changes in the temperature about them.—Ed.) All these facts demonstrate that changes in the external conditions are not the sole factors which produce the sunstroke. The mechanism for losing heat is undoubtedly less efficient in some individuals than in others; and, in so far as the heat-stroke depends upon an insufficiency of heat elimination, it bears a certain resemblance to true fever.

Heat Regulation in Fever.—The cause of the high temperature of fever must be some disproportion between the

production and the loss of heat in the body. Theoretically, fever might be caused either by an excessive heat production without a corresponding increase in the heat loss, or by a diminution in the heat loss without a corresponding diminution in the heat production. We now purpose considering which of these conditions actually exists in fever, and whether or not all cases of fever are produced in the same manner.

Two general methods have been employed to determine the amount of heat produced in the body. In the first, the amount of heat lost has been directly measured in a calorimeter (direct calorimetry); in the second, the products of combustion have been determined and the heat produced calculated (indirect calorimetry). The two methods have been shown to yield identical results in the healthy animal,[31] and we have every reason to believe that the results would also be the same in fever, although this has not yet been definitely proved on account of technical difficulties.[32]

Heat Production in Fever.—In the vast majority of all fevers the production of heat is increased. This has been proved for different diseases of man,[33] such as pneumonia, typhoid fever, pleurisy, erysipelas, tuberculin fever, etc., as well as for various septic diseases of animals, and for fevers produced experimentally by injections of bacteria and various chemical substances.[34]

This increase in heat production is seen both at the time when the temperature is rising and at the height of the fever. It is greatest of all during the chill which initiates so many infections, obviously on account of the violent muscular contractions that take place at the time. During the height of the fever, it is found to be the most marked in those who breathe violently, from whatever cause—here also because of the excessive muscular exertion. If we eliminate these cases, in which the heat production is accelerated by muscular activity, then the increased production of heat in fever usually amounts to from ten to sixty per cent., the average being about twenty to thirty per cent.

In a small number of cases no apparent increase of heat production above the normal limits can be demonstrated.[35] Such observations have been made, for the most part, upon patients in whom there

was but little fever, or in whom the fever was long-continued. In the latter class of cases, it is necessary to remember that the organism tends to limit its metabolism in long-continued illnesses, so that although the quantity of oxygen consumed by these patients with fever may not have exceeded the normal limits, it was in reality above what would have been consumed had no fever been present. In such cases, comparative determinations should be made upon the same individual during periods of fever and of apyrexia; for I do not believe that the possibility of fever without an increase of heat production has been definitively established.

In still another class of cases, high fever may be associated with an unusually low production of heat, *viz.*, when there is a tendency to collapse. As we shall see later, a diminution in the heat production is one of the characteristics of collapse, and even when a tendency to this condition is present, the heat production may be lessened.

Thus we see that in the great majority of all cases of fever, and especially in fevers of short duration, the production of heat in the body is increased. This increase is most marked at the beginning of acute infectious diseases; while in chronic wasting diseases the heat production tends to become limited, and when the temperature is falling it may even be less than normal.

As we have said, the average increase in the heat production in fever is about 20 to 30 per cent. Such an increase is not extraordinary when we remember that Rubner was able to increase the heat production in dogs sixty per cent. solely by feeding them with large quantities of proteid food, and that in severe muscular exertion the heat production may be several times as great as during rest. Normally, the body can dispose of much larger amounts of heat than are liberated within it during fever, so that the cause of the high temperature in fever cannot be an increased production of heat alone.

Indeed, a portion of the increase in heat production is due to the elevation of the body temperature itself, for we know that oxidative processes in general are accelerated by heat. Pflüger has estimated that for every increase of 1° C. in a rabbit's temperature, its heat production increases about six per cent.; and the same has been shown to be true when the temperature of man is artificially ele-

vated.[36] Thus we see that an increase of heat production, amounting to about twelve to eighteen per cent. of the normal, might easily be regarded as an effect rather than as a cause of the increased bodily temperature. The excessive heat production in fever, therefore, may be explained in part as a result of increased muscular movements and in part as the result of the higher temperature of the body. The remaining increase in heat production is very slight, especially if it be compared with that which results from violent exercise or from the ingestion of large quantities of proteid food.

Heat Losses in Fever.—During the rise of temperature the loss of heat from the body is almost always found to be diminished, the losses by radiation and conduction from the skin being especially limited. The amount lost by evaporation of water is frequently increased, however, for, even at this period, the metabolic processes in the body may be accelerated. Yet the increased loss by evaporation does not neutralize the decrease in loss by conduction and radiation; and often, furthermore, the loss of water is also less than normal. Thus, at the onset of fever, the animal utilizes all the means at its disposal to raise its temperature, the production of heat being increased and the losses diminished.

The loss of heat from the surface of the body is regulated mainly by the contraction of the cutaneous blood-vessels. At the onset of many diseases, these vessels contract excessively, and, as a consequence, the skin becomes cold and either pale or cyanotic. This cooling of the skin produces in turn a sensation of cold throughout the body and sets in motion the chemical mechanism already referred to (p. 389), which increases the heat production within the body. Clonic muscular movements, giving rise to the so-called chill, are a consequence. During the chill the temperature rises rapidly to a great height, for the muscular movements greatly increase the heat production, and, at the same time, the heat losses are reduced on account of the contracted cutaneous arteries. That these muscular contractions are due primarily to the coolness of the skin is proved by the fact that if the skin of these patients be warmed the "chill" ceases. Such chills are particularly characteristic of some diseases, and it seems probable that the agents

which cause certain fevers show a special tendency to produce a constriction of the cutaneous vessels, and consequently a chill.

In the great majority of cases the total loss of heat is increased at the height of the fever. This is necessarily true when the heat production is increased, and the temperature is constant, for it is obvious that if the extra heat produced were not immediately given off the temperature of the body would be raised.

In animals, the acceleration in heat losses affects conduction, radiation and evaporation, all to about the same degree, so that the ratio between the first two and the third remains practically the same as in health, *i.e.,* the loss by evaporation amounts to about sixteen to seventeen per cent. of the total loss of heat.[37] In my opinion, however, we are not permitted to infer from this that sufficient evaporation from the body takes place in fever, for it has been shown that if the heat production be increased by other means, the losses by evaporation are relatively much more increased than are the losses by radiation and conduction.[38]

In man it has been found that while the temperature is rising, the elimination of water from the skin approaches the lower normal limits, whereas at the height of the fever it is about fifteen per cent. above normal.[39] During a fall in temperature, it is increased in proportion to the rapidity of the fall. The taking of food markedly increases the evaporation from the skin, both in the healthy and in the feverish. The elimination of water from the lungs is increased proportionately to the greater volume of air used.

In conclusion, it may be said that at the height of a fever the heat losses vary with the heat production, but always remain somewhat less, so that an increase in the temperature of the body is the result.

The conduction and radiation of heat from the skin are governed mainly by the amount of blood that traverses the cutaneous capillaries, and, since the latter are usually dilated at the height of the fever, the skin is ordinarily reddened at this time. Yet many questions concerning the cutaneous vessels in fever are still unsolved. They certainly respond excessively to stimulation, either mechanical or thermic, and for this reason, fever patients easily become chilled when exposed to a draught

of air, etc. Animals with fever also react excessively to reflexes which affect the cutaneous vessels through the medulla.

Many have held that the cutaneous vessels of fever patients are subject to frequent and rapid variations in their state of contraction. This is certainly not always so, however, for, though recent and careful observations on animals have shown that during the rise of temperature considerable variations in the heat loss may take place, the same is by no means true during the height of the fever. Furthermore, there are no very marked variations in the skin temperature of man during typhoid fever, rheumatic endocarditis and many other conditions.[40]

For a better understanding, therefore, of the mechanism governing heat losses as a whole, we require, in addition to our knowledge that the loss by evaporation is small, quantitative studies bearing on the losses by radiation and conduction.

The heat loss during the fall of temperature differs under different conditions. When the fall of temperature takes place by crisis, the loss of heat is greatly increased by the sweating and by the increased radiation and conduction from the skin. When the fall of temperature takes place very gradually, however, the heat loss is often very slight. In such cases the fall is due mainly to a diminished heat production, as has been definitely proved for animals, and as is probably equally true for man. In the majority of cases, however, the fall of temperature seems to be due to a combination of diminished heat production and increased heat loss. Sweating, even in febrile cases, does not necessarily produce a fall in temperature.[41]

Metabolism in Fever.—During the rise of temperature, as well as during the height of the fever, the oxidative processes in the body are usually increased.[42] They run parallel to the heat production, and, indeed, may be used to measure heat production (indirect calorimetry), providing that we know what compounds are being oxidized and what the end-products are. Chills and rapid respirations, *i.e.*, muscular activity, greatly accelerate the metabolism, and a high temperature will do the same. In some cases of fever, however, there is no apparent increase in the metabolic process (p. 392). No strict parallelism exists between the rate of decomposition and the elevation of temperature;[43] and many in-

fections run their course with comparatively slight fever and yet with relatively rapid rates of oxidation.

On the contrary, we occasionally meet with cases, which despite their febrile character seem to exhibit no increase in oxygen consumption. Such a finding nevertheless does not warrant the assumption that the oxidative processes are not accelerated. It is true that brief observations made during fevers which have persisted over a long period will, as the days go by, show a gradual diminution in nitrogen elimination, oxygen combustion and sweat secretion—or, in other words, a lessened heat production and heat loss—but figures thus obtained are not an accurate criterion of metabolic processes during the fever as a whole. Short periods of observation must also take into account how metabolic conditions vary with the stage of the fever. The conception is prevalent, nevertheless, that there are occasional cases in which during the febrile course the oxidative processes are not increased.[44] I cannot convince myself, however, that these will bear a rigid scrutiny, for, as I have already said, we must adhere to the maxim that in fever heat production is increased.

Recent studies have given us a fairly comprehensive knowledge of the substances which are decomposed in fever. In all but the milder cases of infection, the febrile patient is undernourished. Because of his loss of appetite, he generally takes insufficient food unless special measures are resorted to.[45] Yet he needs more nourishment than the normal individual, because of the energy consumed in the increased heat production. For the same reason, his decomposition processes exceed those of a normal person on the same dietetic régime. Nor do the kinds of substances which are decomposed differ in any way in the two cases. It is true that the febrile patient in a fasting condition decomposes more proteid than does an individual in a state of inanition, but with no infection or fever; yet so far as the total consumption of energy goes, the percentage of nitrogen excreted runs parallel in the two. If the patient with fever be given an adequate diet, his nitrogen equilibrium will be maintained and his strength conserved.[46] Herein lies the difficulty, for such patients are almost always in a state of inanition due, on the one hand, to their anorexia and, on the other, to their greater

caloric need. The combination of diminished caloric intake and increased caloric need explains the high proteid decomposition ordinarily observed in fever.

The rapidity of proteid consumption varies in different infections and with the stage of the disease. Furthermore, it is quite independent of the height of the fever.[47]

The decomposition of proteids to their ordinary end-products accounts, in part, for the increased production of heat in fever, but as this source is inadequate, non-nitrogenous substances are utilized just as is the case in starvation. Glycogen plays an insignificant rôle, because it is rapidly consumed, and further because it is not stored up to any great extent in fever.[48] Fat, therefore, must provide the remainder of the energy required.[49] In brief, metabolism in fever follows the same laws as in starvation, as is evidenced by the fact that the respiratory quotient in the two states—the nourishment being the same—is identical. The abnormally low quotient formerly frequently observed in febrile patients we now know to have been based upon too short a period of observation.[50]

The augmented proteid combustion in fever is due, in part, therefore, to the associated inanition, and in part to the generally increased production of heat. We have already noted that fever *per se* accelerates the processes of combustion, and in this the tissue proteids also naturally take part. So far as man is concerned,[51] it has been shown that if the temperature is artificially raised to 39° C. the proteid decomposition is not affected; whereas, if the temperature reaches 40° C., an increase in proteid destruction is said to take place. In these investigations, however, the total consumption of energy has not been taken into consideration.

Nor does proteid destruction take place along different lines from those in simple inanition.[52] The formation of albumoses is not of frequent enough occurrence to be looked upon as characteristic of fever, as was formerly supposed.[53] Most of the end-products of proteid decomposition that appear in the urine do not differ qualitatively from those present in health. Thus the urea is relatively reduced and the ammonium salts of organic acids increased. The increase in the amount of these organic acids in the blood is the probable cause of the diminution in the amount of carbon dioxide that is present there.

As a rule, the creatinin is also increased in the urine. We have no positive information as to the amount of uric acid formed during fever.

That the amount of heat set free in fever by the processes of combustion corresponds to that determined by direct calorimetry, is evidence, in my opinion, of the contention that the excess of heat which is generally produced in fever arises solely from chemical decompositions, just as does the total heat production in the normal individual. In other words, there is no special mechanism of heat production in fever. The view [54] that heat is produced in fever by peculiar processes of hydration can be discarded, for the accumulation of water in the tissues during long-continued fevers does not differ from that in cachectic conditions unassociated with fever. Indeed, in the process of hydration, heat is utilized, not set free.[55]

The Cause of the High Temperature in Fever.—We have already said that a rise in temperature must always be due to a disproportion between the heat production and the heat loss in the body. Since the production of heat in fever is greater than in health, it is theoretically possible that this increased production of heat may be the sole cause of the high temperature. Yet we know that large amounts of heat may be produced in the normal individual by muscular exertion, and that these do not ordinarily cause any marked rise in temperature. It might be urged, therefore, that in fever the fault lies in the mechanism which regulates the heat loss, or, in other words, that the heat in fever is produced in such a manner that it does not furnish the normal stimulus to the mechanism that increases heat loss. This would be an acceptable theory were the mechanism of heat production in fever different from that in the healthy person; but as this is not the case we are in no position to say whether the mechanism which increases the loss of heat from the body is relatively inactive or not. We would emphasize the fact, however, that there exist no grounds for such an assumption.

The Site of the Heat Production in Fever.—The character of the metabolic changes in fever gives us no definite idea as to the tissues especially affected, for, as we have seen, the urine contains only such decomposition products as appear when there is cellular destruction of any sort in the body. The evidence

in favor of an increased consumption of red blood-corpuscles is very inconclusive. Neither the increased amounts of potassium salts in the urine nor the abnormal pigments there present can be considered to prove a widespread destruction of these elements; and the blood-picture itself is inconsistent with such a conception.

Observations on the temperature of the blood returning from various parts of the body do, however, give us some data as to the site of the heat production. Heidenhain and Körner found that when artificial fever had been produced in dogs by the injection of pus, the blood returning from the legs was warmer than that in the right ventricle.[56] Numerous other observers[57] have since shown that, in artificial fever, the venous blood returning from the kidneys, and especially from the liver, is warmer than that from the muscles and the skin. From these observations, we may infer that the excessive heat of fever is produced mainly in the large glands and the muscles; but to what extent each of these participates in its production is very uncertain.

Since the glycogen of the body is consumed during fever,[58] and since the artificial fever produced by puncture of the brain likewise brings about a consumption of glycogen—and indeed occurs only when there exists a store of glycogen in the body[59]—it seems highly probable that the cause of the increased heat production in ordinary fever is a stimulation of the central nervous system, similar to that induced by the puncture.[60]

The Heat-Regulatory Mechanism in Fever.—In the healthy individual, a proper heat regulation cannot be maintained unless certain parts of the mid-brain are intact. If these parts of the brain be destroyed, or if the spinal cord be cut at a high level, then the temperature depends largely upon that of the surroundings, just as it does in the case of cold-blooded animals. Though the exact location of these heat-regulating centres is not known, it would appear from the studies of Isenschmid and myself that the basal ganglia are of fundamental importance in this regard.

It would seem probable that this nervous mechanism which regulates the temperature of the body is diseased in fever. The observations bearing on this question have dealt, for the most part, with the effect of procedures which withdraw heat from the body;

and experiments on men as well as animals have shown that if heat be artificially withdrawn from the body by cold baths, etc., the compensatory increase in the heat production is less if the animal has a fever than if it be normal. In certain experiments on animals, indeed, there may be absolutely no increased production of heat under these circumstances.[61]

It follows that the temperature of febrile animals is more readily reduced by artificial cooling than is that of normal animals, and that, other things being equal, the patient with fever may be cooled off with comparative ease. It is also probable that his temperature may be more easily raised by artificial means. For example, animals more readily acquire a high temperature from warm surroundings if they have been previously treated with injections of pus.[62] In apparent contradiction to these facts is the observation that the temperature of an animal with fever is sometimes made higher by exposure to cold, possibly because the cold increases the heat production within the body.

It is evident, therefore, that in fever the organism reacts qualitatively to a cooling or heating of the body surfaces like a normal animal. Quantitatively, however, there exist differences, in that in pyretic conditions the response to external changes is not so prompt or so complete. Furthermore, conditions are similar in fever states with respect to the heat which the animal itself produces. Thus weakly individuals, tuberculous patients and those running a slight temperature or convalescing from an infection, often exhibit fever after muscular exertion or after heavy meals.[63] In the case of typhoid fever and tuberculosis, a diet of high caloric worth ordinarily causes no rise in temperature, probably because the heat loss is increased by evaporation from the skin.[64] Though the latter is not so great as in health, it serves nevertheless as an efficient regulatory factor.

We may say then, at this point, that *though heat regulation is maintained in fever, the regulatory apparatus is less responsive than in health to certain demands made upon it.*

It is a matter of common clinical experience that *the temperature of patients with fever is less resistant to external influence than is that of normal individuals.* This lack of resistance differs in amount in different diseases and may even vary at different periods of the

same disease. During typhoid fever, for example, the temperature can usually be reduced more readily in the later than in the earlier weeks of the illness. One reason why fever patients are particularly susceptible to the antipyretic action of the cold bath is that their cutaneous vessels react abnormally to stimuli. It is when these vessels remain dilated for a considerable period after the cold bath that the most marked falls in temperature occur.[65] The antipyretic drugs also reduce the temperatures of fever patients much more effectually than they do those of normal individuals;[66] and here again these drugs are not equally effective in all cases nor in the same case at all stages of the disease. Thus we see that the temperature does not resist external influences during fever so well as it does during health, partly because the regulatory mechanism is less effective, and partly because the peripheral blood-vessels react abnormally to stimuli.

Even during the convalescence from infectious diseases, the temperature regulation is often imperfect. Patients who are recovering from typhoid fever, for example, easily acquire an elevation of temperature after eating large amounts of food or after excessive exercise, apparently because they cannot eliminate the large quantity of heat that has been suddenly liberated in their bodies. An analogous condition is seen in many captive animals, and it seems as if their temperature regulation were injured to a certain extent by the life of captivity. Thus Finkler has observed a temperature of 40° C. (104° F.) in starving guinea-pigs after a full meal.

In view of the fact that the temperature is elevated in fever, and that heat regulation is maintained, it may be said that conditions are to a certain extent correctly described by Liebermeister's formula, *viz.*, that the heat-regulatory centre in fever is "set at a higher level." This hypothesis is at present so widely accepted because of the current tendency to regard each natural process—in this case, fever—as essential to the life of the individual.

This formula represents the facts in so far as it concerns heat regulation. But there is more to fever than a mere regulation of heat; otherwise in febrile states we should expect to find only the evidences of this "higher-pitched" regulation. This, however, is rarely the case. First and foremost, fever is generally, in my opinion always, associated with an enormously increased

heat production. The adherents of Liebermeister's theory meet this objection by observing that the symptoms accompanying the new level of regulation vary with the cause of the fever. Though this is to a certain extent true, such associated symptoms, *e.g.*, an increase in heat production, are actually a part of the febrile process. This applies equally well to fever produced by chemical means, in which case an infection plays no part. It is true that in bacterial affairs, the micro-organisms are capable of augmenting the decomposition processes, possibly without at the same time causing fever. This has definitely been shown to be the case among cold-blooded animals in which fever cannot be produced because there is no mechanism of heat regulation. As for warm-blooded animals, the effects of febrile infections have been little studied. It is highly probable, however, that the microbic agency itself may be the cause of the increased decomposition processes, and to this extent the protagonists of Liebermeister are justified in assuming that it is difficult, perhaps impossible, to separate the consequences of infection from those of fever. But this reasoning is not applicable to the so-called aseptic fever which occurs after the injection of albumoses or following blood extravasations into the tissues. Here, too, there is an increased production of heat and this increase is not a direct effect but associated with the symptom-complex of fever.

Heat regulation is a complex process, bringing into play factors which act independently upon heat production and heat loss. Loss and production are regulated under different conditions by different physiological tools; the former by conduction, radiation and evaporation, and the latter by the decomposition of the constituents of the food or of the tissues. In my opinion, fever brings about an alteration in all the various components of this mechanism, though the extent to which each is affected varies with the case. The faculty of regulation is, on the whole, preserved. I am of the opinion that there exists always a hyperstimulation of those places which have to do with heat production, or, in other words, a peculiar linking of disturbed heat production and heat elimination.[67] The centres for the regulation of the latter are variably affected, but on the whole they are inefficient. In this particular we are agreed with Liebermeister, *viz.*, that the regulatory function in its entirety is "higher pitched." But conditions vary

greatly in different cases. The cutaneous vessels may be constricted or dilated. Sweating is always present to some extent, and oftentimes greatly increased—not infrequently, indeed, during a chill. This variable behavior of the centres depends upon the nature and virulence of the infection, upon the constitution of the patient and upon the stage of the disease.

The explanation of the different phases of the febrile process resides, therefore, in the behavior of the heat-regulating centres in the brain, upon which the hypothetical fever-producing substances are assumed to act. We have already discussed the facts for and against the conception of a single substance being responsible for all fevers. In view of Friedberger's epochal work on anaphylatoxin, we are in a better position to answer this question. The irritability of the heat-regulating centre is unquestionably subject to great variations, being particularly susceptible to chemical actions and infectious processes. Friedberger[68] has made quantitative studies of the effects produced by reinjection in animals sensitized with foreign proteids. Small doses of the specific proteid caused fever; while collapse, with subnormal temperature, and even death, followed the injection of larger amounts. Friedberger's observations are based upon specific reactions which are of genuine anaphylactic nature. In this sense, fever may be looked upon as the most delicate response of a sensitized animal. The doses necessary to cause the rise in temperature are incalculably small. Furthermore, Friedberger was able by varying his dosage to produce every known type of fever curve. Though anaphylatoxin is not a specific substance, its mode of origin is specific; and as such it might be looked upon as the uniform cause of infectious fevers, producing the latter by stimulation of the heat-regulating centre.

The Nutrition in Fever.—The nutrition is always impaired in fevers of long duration, because, as we now know and as we have already noted, the patients do not take a sufficient quantity of food. Their appetites are often very poor, though this may not be the case in the hectic fever of tuberculosis. For these reasons most patients with fever become emaciated and weak, and the weakness is often greater than can be accounted for by the lack of food alone, being dependent, as we have seen,

upon the excessive consumption of both the proteid and non-proteid materials of the body.

On the other hand, in long-continued infections, a tendency to limit the metabolic processes is often manifest, and in the terminal stages of chronic diseases the proteid decomposition and the total oxidations in the body often reach a surprisingly low level. This adaptation enables many a person to undergo a long-continued illness which would otherwise prove fatal. Though the excessive consumption of proteid material is common to all forms of fever, it seems very probable that certain infections are particularly harmful in this respect.

The cause of the various forms of cellular degeneration that occur so frequently in fever is not yet definitely determined. Some believe that the high temperature may cause the degenerative changes,[69] whereas others hold that the temperature alone will not produce them.[70] It is impossible at present to reconcile these varying views.

The Water Retention in Fever.—Years ago Leyden[71] made the observation that patients with fever frequently lose but little weight during the course of the acute process—*i.e.,* at the time when the consumption of material in the body is most active—but that the principal loss in their weight takes place during convalescence. He explained these results by assuming that there is a retention of water in the body during fever. From that time up to the present this question has awakened general interest.

In its discussion one might distinguish between an absolute retention of water and a mere relative retention, *i.e.,* an increase in the proportion of water in the tissues. So far as an absolute retention is concerned, this is not caused by a high temperature or by the infection itself. Only when the kidneys or heart are diseased is there an absolute insufficiency of water elimination during fever. In general, there is no absolute decrease in the excretion, but on the contrary a slight increase, corresponding to the increased rate of metabolism. The diminished urine which is so often seen in the early days of an infectious disease is compensated for by an increased evaporation of water from the skin and lungs. The increased urine during defervescence, as occurs, for example, during the late weeks of typhoid fever, is due to the fact that at this time the sweating sinks to a minimum.[72]

Less heat is eliminated because less is produced in the late stages of long-continued infectious diseases (p. 393).

The relative amount of water in the tissues does not change during fevers of short duration, such as pneumonia, but in long-continued fevers, such as typhoid or tuberculosis, the tissues become relatively rich in fluids and poor in solids. The cause of this seems to lie in the excessive proteid destruction, resembling in this respect the cachexia of carcinoma. A normal individual rapidly excretes any additional water that may be introduced into his body, up to three litres or more per day. Why the patient with fever fails to excrete the extra liquid in his tissues is not known, though we suspect that it is because the extra water is retained chiefly within the cells themselves and does not reach the blood or lymph. To what extent this water accumulation may be due to the retention of nitrogenous substances or to an altered salt metabolism, is at present undetermined.

The Significance of Fever.—Whether or not the elevation of temperature is of advantage to the infected organism is a subject that has engaged the attention of physicians from the most remote times down to the present. Three conflicting views have been advocated. According to the first, the elevation of temperature is in itself dangerous to the patient,[73] and may even be the cause of death; according to the second, the danger of the infectious process depends only to a very slight extent upon the high temperature, and according to the third, the high temperature is advantageous, for by this means the infected body is "cleansed by fire."[74] The treatment of fever must depend, to a large extent, upon the view that is accepted by the physician.

Is the elevation of temperature in the course of an infection useful, harmful or of no particular significance? So long as the elevation remains within moderate limits, it may certainly be regarded as relatively harmless. The rapid pulse and respirations, the loss of appetite and the possible parenchymatous degeneration of the organs, in so far as they are directly caused by the temperature, are not in themselves very dangerous. If, on the contrary, the elevation of tem-

perature is very great, it may undoubtedly be harmful, for the same dangers are threatened as in a heat-stroke. Yet such dangerously high temperatures are comparatively rare in fever; and the reason why a high temperature is generally regarded as a bad sign in an infectious disease is that it indicates a severe infection. This is well illustrated by the fact that high temperatures in malaria are generally regarded with a certain amount of indifference, whereas the same temperatures in rheumatic fever or pneumonia would be looked upon with alarm.

Whether the elevation of temperature is directly beneficial to the infected organism or not, is a question that is not so easily settled. In recent years there has been a tendency to apply the Darwinian theory to pathological processes in general, and to say, for example, that fever could never have survived throughout immeasurable time were it not inherited as a useful weapon in the struggle for existence. Yet one may question to what extent the Darwinian theory applies to pathological conditions,[75] for it seems equally reasonable to regard fever as a blind reaction against an injury, possibly useful or possibly harmful. The question is not one that can be solved by such philosophical considerations, and the final answer must be based upon established facts, derived either from bedside observations or from animal experiments.

Unfortunately, clinical studies have done little to solve this problem. We have, it is true, accumulated extensive statistics on the course of infectious diseases, especially of typhoid fever, under the expectant and antipyretic forms of treatment. Yet, even though we acknowledge the advantage of the latter treatment, we are helped but little to a solution of our problem, for cold water not only lowers the temperature of the body, but it influences the disease in many other ways; and antipyretic drugs introduce abnormal chemical processes into the metabolism, and above all act upon the patient's nervous system and mental condition.

It is possible that at a higher temperature the growth or virulence of the micro-organisms which cause the disease may be diminished. At present, however, we are unable to say definitely to what extent this actually occurs in disease.

We do possess, however, a number of observations on the effect of increasing an animal's temperature after it has been artificially infected. Infection with diphtheria bacilli, chicken

cholera bacilli and pneumobacilli run a milder course in rabbits if the temperature be artificially elevated by puncture of the brain;[76] and intoxications with hydrolytic ferments are also less virulent at higher temperatures.[77] The same has been found to be true for erysipelas infections in rabbits,[78] and the number of such examples could be still further multiplied.

Perhaps the action or formation of antibodies is favored by the high temperature. Kast[79] found that Pfeiffer's antibody against typhoid bacilli was more efficient at higher temperatures; though, on the other hand, antipyretic treatment does not seem to influence the formation of the immune body in man.[80]

We possess, therefore, some noteworthy experiments which support the view that the elevation of temperature during an infection is directly beneficial to the infected organism. It must be admitted, however, that only a beginning has been made, and that more observations are necessary before the question can be regarded as definitely settled, and before we shall know whether it is the increased temperature itself or some associated changes in metabolism that benefit the patient.

The Temperature in Collapse.—We have had frequent occasion to mention that the temperature during fever is subject to great variations, and that it tends to rise or fall from relatively insignificant causes. A great fall of temperature during an infection has long been recognized as a dangerous symptom, mainly because it so frequently heralds the onset of collapse; this has been observed experimentally. The ordinary fever-producing agents may cause a reduction in an animal's temperature if they are especially potent, or if the animals used are very "weak" or "non-resistant." It is difficult to say what constitutes this "weakness" or "lack of resistance" on the part of infected individuals, though it is possible that the condition of the circulation plays an important rôle.

Not only the resistance of the individual, but the kind and quantity of toxins are of importance in the production of collapse. The same substance that will give rise to fever in small doses will lead to collapse if given in large doses. This is well illustrated in the case of Koch's tuberculin.[81] If this substance be given to animals in very large doses, the production of heat in the body is

actually diminished, and in the fatal cases only fifty-three per cent. of the normal amount of heat may be produced. At autopsy, the vessels in the abdomen, and especially those belonging to the intestines, are found to be dilated. This finding agrees with the observations of Romberg, Pässler and Bruhns (see page 86), who showed that the circulatory failure in infectious diseases was principally caused by a central vascular paralysis, affecting especially the splanchnic vessels. The dilatation of these vessels allows so much blood to collect in them that the heart is no longer properly filled from the veins, the general blood-pressure falls, and the activity of the muscles becomes so reduced that, in spite of the fact that the heat losses are greatly diminished, the body is no longer able to maintain its normal temperature. Thus we see that the fall of temperature in collapse occurs at a time when less heat than normal is produced in the body.

A certain antagonism exists, therefore, between fever and collapse. In fever, both the heat production and the heat losses are increased, the former being especially accelerated. In collapse, both of these are diminished, but the heat production is more diminished than is the heat loss. On the other hand, fever and collapse resemble each other in certain respects, for in both too small an amount of blood passes through the cutaneous vessels.[82] Indeed, they tend to shade into each other, and, as we have seen, the one or the other may result from the same cause, depending upon the factors already described. Of interest is the fact that in death from anaphylactic shock, we encounter a similar overloading of the splanchnic vessels (see p. 87).

Subnormal Temperature.—Subnormal temperatures are seen not only during collapse from infectious diseases, but also after extensive injuries, severe hemorrhages, long-continued narcosis, perforative peritonitis and various other severe lesions within the peritoneal cavity. In many of these, the same conditions are present as in collapse, though it is incorrect to regard all subnormal temperatures as symptoms of collapse.[83]

Subnormal temperatures are more common than is generally supposed. They are often seen during convalescence from infectious diseases, and are then generally due to a diminished production of heat combined with an inefficient

heat regulation. A subnormal temperature frequently accompanies intoxications with alcohol or related drugs. These lessen the rate of oxidation in the body, and, in addition, interfere with the mechanism regulating the loss of heat from the skin.[84] Consequently, an intoxicated man is less able to withstand cold than is a healthy individual, and if exposed to cold, the temperature of his body is more liable to fall.

When the temperature of the body becomes very low, narcosis, and finally a general paralysis, result. The narcosis will, in turn, favor a further lowering of the temperature, for the body can no longer increase its production of heat by muscular activity. Even in ordinary sleep the heat regulation is less efficient than during the waking hours, and this lack of regulation is much more marked during deep narcosis. For these reasons, the danger of freezing to death is best combated by continued muscular movements, for these not only increase the production of heat, but they reduce the tendency to go to sleep.

We do not know how low the temperature may fall without causing death, though it is certain that both men and animals have recovered from very low temperatures.[85]

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[51] Linser and Schmid: Arch. f. klin. Med., lxxix, 514.
[52] Mohr: Zeitschft. f. klin. Med., lii, 371.
[53] Morawitz and Dietschy: Arch. f. exp. Path., liv, 88: Schultess, Arch. f. klin. Med., lviii, 315, and lx, 55; Krehl and Matthes, ibid., liv, 501.
[54] Herz: Untersuch. ü. Wärme and Fieber, 1893; Kongr. f. inn. Med., 1896, 86.
[55] F. Kraus: Wiener klin. Wochenschft., 1894, No. 15.
[56] Pflüger's Arch, iii, 562.
[57] Krehl and Kratsch: Arch. f. exp. Path., xli, 185; Hirsch and Müller, Arch. f. klin. Med., lxxv, 287.
[58] Hirsch and Rolly. Arch. f. klin. Med., lxxv, 305; Rolly, ibid., lxxviii, 250.
[59] Rolly: l. c.; for an opposed view, see Senator and Richter, Zeitschft. f. klin. Med., liv, 16.

[60] See Gottlieb, in Meyer and Gottlieb, Pharmacology (Halsey, Philadelphia, 1914, 453).
[61] Liebermeister: Path. d. Fiebers, 341; Colasanti, Pflüger's Arch., xiv, 125; Finkler, ibid., lix, 98; Zuntz, Du Bois Arch., 1882, 43.
[62] Dobrzanski and Naunyn: Arch. f. exp. Path., i, 181; Finkler, l. c.
[63] Penzoldt and Birgelen: Münch. med. Wochenschft., 1899, Nos. 15–17; Ott, ibid., 1901, No. 50, and 1902, No. 38; Schröder and Brühl, ibid., 1902, Nos. 33–35.
[64] Schwenkenbecher and Tuteur: Arch. f. exp. Path., lvii, 285; Lang, Arch. f. klin. Med., lxxx, 353; Lœning, Klin. Jahrb., 1908, xix, 105.
[65] Finkler: Kongr. f. Inn. Med., 1888, 314.
[66] Gottlieb: Arch. f. exp. Path., xxvi, 419, and xxviii, 167.
[67] *Cf.* Schmiedeberg: Grundriss d. Pharmakologie, 4th edit.
[68] See especially, Zeitschft. f. Immunitätsforsch., x, 1; Münch. med. Wochenschft., 1910, Nos. 50 and 51.
[69] Liebermeister: Path. d. Fiebers, 427.
[70] Naunyn: Arch. f. exp. Path., xviii, 49.
[71] Arch. f. klin. Med., v, 366.
[72] Schwenckenbecker and Inagaki: Arch. f. exp. Path., liv, 168.
[73] Liebermeister: Path. d. Fiebers, 423; Krehl, Ergeb. d. allg. Path., 1896, 409.
[74] Pflüger: Pflüger's Arch., xiv, 502; Unverricht, Volkmann's Vorträge, N. F., No. 159.
[75] See Ziegler: Münch. med. Wochenschft., 1896, No. 43.
[76] Loewy and Richter: Virch. Arch., cxlv, 49.
[77] Hildebrandt: Virch. Arch., cxxi, 1.
[78] Filehne: Jour. of Phys., xvii (Proc. Physiol. Soc.).
[79] Kongr. f. inn. Med., 1896, 37; Paech, Diss. Breslau, 1900; Rolly and Meltzer, Arch. f. klin. Med., xciv, 335; Lüdke, ibid., xcv, 425 (lit.).
[80] Lemaire: Arch. internat. de pharmacodyn., v, 225; Schütze: Zeitschft. f. Hyg., xxxviii, 205.
[81] Matthes: Arch. f. exp. Path., xxxvi, 437; xxxviii, 299; Krehl, ibid., xxxv, 222.
[82] Maragliano: Zeitschft. f. klin. Med., xiv, 309; xvii, 291.
[83] Janssen: Arch. f. klin. Med., liii, 247.
[84] Rumpf: Pflügers Arch., xxxiii, 538.
[85] Janssen; l. c.; Cohnheim, Allg. Path., 2nd edit, ii, 489.

CHAPTER XI

THE SECRETION OF URINE

THE major portion of the solid waste products that arise in the body leaves it by way of the kidneys. As we have already had occasion to describe many of these substances, it is not our purpose to review in this place the origin of each, but rather to deal with the mechanism of secretion itself; though it must be admitted that it is often impossible to draw a sharp line between the secreting mechanism and the products that are eliminated.

The composition of the urine depends partly upon the condition of the secreting cells in the kidneys and partly upon the quality and quantity of blood which passes through these organs. These factors are more or less interdependent one upon the other. For example, if the blood-stream through the kidneys be slowed, not only does less blood come into contact with the secreting cells, but the latter are liable to suffer in structure and function. On the other hand, if the renal cells are primarily injured, this frequently affects the circulation through the kidneys. It is often very difficult, therefore, to tell which part of the renal apparatus is primarily involved.

The Effect of an Increased Flow of Blood through the Kidneys.[1]—It is a general rule that the quantity of urine secreted varies directly with the quantity of blood that flows through the kidneys. It varies likewise with the difference between the pressure of the blood in the capillaries and the pressure of the urine within the uriniferous tubules. When the total quantity of urine is increased, the percentage of solid materials decreases, and *vice versa;* yet this percentage of solids nearly always remains within certain limits, rarely going above twelve per cent. or below three-tenths per cent. The relation between the total quantity of solids excreted and the total quantity of urine seems to be subject to considerable variation; and the different solids often vary independently of one another.

Whenever more blood flows through the kidneys, therefore, the amount of urine is increased. The cause of the increased blood-flow may lie either in a higher arterial pressure, unaccom-

panied by a corresponding contraction of the renal vessels, or it may be due to a local dilatation of these vessels, while the general blood-pressure remains constant.[2]

Many forms of chronic nephritis are accompanied by a high blood-pressure (see p. 25), and this always causes an increased secretion of urine, if a sufficient number of functioning renal cells are present, and if the increase in the general blood-pressure is not accompanied by a constriction of the renal vessels of such a degree as to prevent a more rapid blood-flow through the kidneys. As we have said, the increased elimination of water in such cases reduces the percentage of solids in the urine. The absolute excretion of the different solids, however, in these forms of nephritis varies greatly,[3] being dependent, apparently, to a great extent upon the condition of the epithelial cells. On the other hand, an increased secretion of urine in chronic nephritis is less frequent than is generally believed, occurring according to one observer[4] in only one-third to one-half of the cases. The increased blood-pressure that follows the administration of digitalis to patients with heart disease also frequently causes an increased elimination of urine, because the renal circulation is improved.

Diabetes Insipidus.—The second condition leading to an increased flow of blood through the kidneys is a local dilatation of their vessels, the arterial pressure remaining constant. This can be experimentally proved by cutting the renal nerves.

Such a dilatation of the renal vessels is a possible cause of diabetes insipidus,[5] a disease which is characterized clinically by the excretion of large amounts of dilute, sugar-free urine, without an associated increase in the general arterial pressure. The excessive amount of urine frequently carries out with it demonstrable quantities of inosite, and at times the total quantity of nitrogen is also increased. This latter increase is caused in part by the large amounts of meat eaten; for many of these patients, for some unknown cause, have excessive appetites, just as have patients with diabetes mellitus. In those cases of diabetes insipidus in which an abnormal appetite is associated etiologically with an excessive thirst—and into this category falls the majority of cases—the suspicion is strong that we have to do with a polydipsia of psychic origin. The evidence that disturb-

ances of proteid metabolism occur in diabetes insipidus is not convincing, nor is it likely that such do occur.[6]

We really know very little concerning the etiology of diabetes insipidus. It unquestionably occurs at times as a family disease. Syphilis also plays an etiological rôle. In some cases, anatomical lesions of the cerebellum, the pons or the medulla have been found—findings which accord well with the experimental observation that injuries to corresponding parts of the brain may lead to polyuria.[7] Yet there is some uncertainty as to the exact part of the brain that must be affected in order to produce this increased flow of urine, and further as to the manner in which such an injury brings about the polyuria. In some cases the evidence at our disposal points to a disturbance of the vasomotor system, leading to a local dilatation of the renal arteries. Such an hypothesis, however, would scarcely explain all of the clinical manifestations.

Oftentimes it is impossible to say whether the polydipsia or the polyuria is primary, for the former may also be due to certain cerebral lesions. There is little doubt, however, as we have noted above, that some of the cases diagnosed as diabetes insipidus are in reality instances of psychic polydipsia. To the latter belong those severe cases passing twenty or more litres per day; further, those in which the individual is addicted to the drinking of abnormal fluids, such as urine; and finally those in which water alone is capable of assuaging the thirst.

The characteristic feature of the disorder, according to Meyer, is in some cases the inability of the kidneys to excrete a urine of normal concentration,[8] because of which a polyuria is of regulatory significance in removing the waste products of metabolism. In such cases a disturbance of the renal epithelium must be assumed; while in others, in which the kidneys have not lost the power of delivering a concentrated urine and in which the increased thirst is the prominent symptom, the polyuria would seem to be due to an abnormal dilution of the blood. It is evident, therefore, that what we term diabetes insipidus is not of uniform etiology.

(Clinical and experimental data point strongly to the etiological importance of the hypophysis in diabetes insipidus. The frequent association of the disease

with lesions of the base of the brain and interpeduncular space—especially with basal gummatous meningitis—is well-recognized. A more critical study has shown that such lesions often involve, or are restricted to, the posterior lobe of the pituitary body.[9] In keeping with these findings is the presence in the posterior lobe of a diuretic substance distinct from the pressor body it contains (Magnus and Schafer). Lewis and Matthews[10] were able to produce a transient polyuria in dogs in one-half of their cases by operative procedures. From the fact that the most constant finding in those animals exhibiting a polyuria was a remnant of the epithelial covering of the posterior lobe, the pars intermedia, they have concluded that diabetes insipidus is due to a hypersecretion of the diuretic substance of the posterior lobe, this substance being the product of the epithelial cells of the pars intermedia—Ed.)

Under pathological conditions, we frequently see transitory increases or diminutions in the secretion of urine—increases in hysteria, after epileptic convulsions or after ureteral catheterization, diminutions in these same conditions or after operations on, or injuries of, the kidneys. It seems probable that many passing variations in the secretion of urine are caused by circulatory disturbances in the kidneys which are of reflex origin.

The Effect of a Diminished Flow of Blood through the Kidneys.—If the quantity of blood that flows through the kidneys be diminished, a small amount of highly concentrated urine is secreted; in other words, the diminution in the total solids does not parallel that of the water.

The cause of such a diminished blood-flow may be either local or general. Locally, a contraction of the renal vessels will diminish the renal circulation, and it may do so even though the general blood-pressure be increased from a contraction of many other arteries. This local constriction of the renal arteries is the cause of the diminished secretion of urine in asphyxia, in strychnin and epinephrin poisoning[11] and in epileptic and eclamptic convulsions.

In the second place, a diminished renal circulation may occur in the absence of any local constriction of the renal vessels, either because the general arterial pressure is reduced or because the pressure in the renal veins is raised. The reduction of the general arterial pressure may

result from a widespread vasomotor paralysis or from a weakening of the left ventricle. The pressure in the renal veins may be raised, either by an occlusion of these veins, or of the vena cava inferior; by an increase in the general venous pressure from a weakening of the right ventricle; or by a diminution in the aspirating action of the thorax. The most marked effect upon the renal circulation will naturally be produced when a lowering of the general arterial pressure is combined with a rise in the venous pressure. This combination occurs when both ventricles are weakened, and this is indeed the most frequent cause of an insufficient flow of blood through the kidneys. It is met with in many varieties of cardiac disease, whether these affect the endocardium, the myocardium or the pericardium.

Aside from cases of cardiac stasis, a diminished amount of urine is observed most frequently in the acute nephritides, a finding in keeping with the fundamental pathological fact that the blood-stream is slowed in inflamed tissues. In human nephritis, however, it has always been a matter of comment that the clinical manifestations are often out of all proportion to the anatomical changes in the kidneys. Schlayer and Takayasu[12] have thrown considerable light upon this subject by showing that even the most trivial glomerular lesion may cause severe disturbances of urinary secretion and of the ability of the renal vessels to contract and dilate.

This impairment of the vessel function occurs chiefly in the so-called vascular nephritides, though the tubular types are not unaffected in this respect. In all inflammatory renal processes, therefore, a disturbance of vascular integrity must be taken into account, whether the glomeruli exhibit a characteristic swelling of the epithelium, or seem to be normal. The disturbance may cause either a lowered vascular irritability, in which case the urinary secretion is diminished, or an augmented irritability leading to an increased secretion. This behavior of the vessels applies not only to the experimental nephritides, but also to acute and chronic cases in man.

In many of these circulatory disturbances, proteids from the blood pass through into the urine; yet, since this is probably due to changes in the epithelial cells, we shall defer its consideration to another place.

The Effect of an Obstruction to the Escape of Urine.—The obstruction to the escape of urine may be situated within the kidney itself. The uriniferous tubules may be compressed by scar tissue, or their lumina may be occluded by casts or by precipitates of hæmoglobin, bilirubin, uric acid, calcium salts, etc. It is questionable, however, if such precipitates, with the exception of hæmoglobin, really offer much resistance to the escape of urine; and it is quite possible that they lie in the tubules merely because the amount of water secreted is insufficient to carry them away.

On the other hand, the obstruction to the exit of urine may be situated outside of the kidneys, in the lower urinary passages, in which case it may be caused by calculi, tumors, scar tissues, etc. The effect of such obstructions upon the total quantity of urine secreted depends, in the first place, upon whether they hinder the outflow from one or from both kidneys. If the former be the case, the affected kidney will eliminate less urine than normal, but the urinary material retained in the blood will stimulate the other kidney and cause it to do extra work and to hypertrophy. The urine, as a whole, therefore, will not be greatly altered.

The effect of an obstruction upon the secretory activity of the affected kidney depends largely upon the degree of obstruction.[13] If this be so complete that the urine is retained under a pressure amounting to sixty millimetres of mercury or more, the affected kidney ceases to secrete.[14] If the obstruction be less complete, so that the urinary pressure above the obstruction be less than sixty millimetres, the secretion continues, the rapidity of secretion diminishing in proportion to the increase in pressure of the retained urine.[15] The details concerning the cessation of secretion are not very well understood. At first, the retained urine merely serves to distend the urinary passages. As the pressure increases, however, a portion of the urine appears to be resorbed through the cells of the urinary tubules, which then become œdematous. Finally, the overfilled tubules and the swollen cells press upon the veins and capillaries, thereby diminishing their size and lessening the rapidity of the flow of blood through the kidneys. This, in turn, diminishes the secretion of urine.

If the obstruction to the flow of urine from a kidney

be complete and permanent, the corresponding kidney atrophies, and only a moderate grade of hydronephrosis develops. If, however, the obstruction be incomplete, or if it be more or less intermittent, the structure and the function of the kidney are but little affected. Its pelvis, however, gradually dilates, and an enormous hydronephrosis may be produced.

The Effect of Lesions of the Secreting Membranes.—We have already mentioned the susceptibility of the renal epithelium to changes in the quantity and quality of blood that passes through the kidneys. Several membranes separate the blood in the capillaries from the lumina of the uriniferous tubules, viz., the capillary walls, the basement membranes and the epithelial cells. The possibility exists, therefore, that lesions of any one of these might render the secretory apparatus abnormally permeable. Apparently, however, lesions of the capillary walls are of comparatively little importance; and it may be said in general that the secretion depends rather upon the parenchyma cells than upon the endothelial lining of the capillaries. Indeed, widespread amyloid degeneration of the renal capillaries has been observed without resultant changes in the urine. It must not be overlooked, however, that so far as the epithelial constituents of these secreting membranes are concerned, different substances in the urine are eliminated by different renal structures.

All lesions of the epithelial cells, degenerative as well as inflammatory, and especially those which involve the glomeruli, tend to diminish the secretion of water. Yet, in many cases of nephritis this tendency is more than neutralized by an associated increase in the amount of blood that flows through the kidneys, for, as we have seen, this tends to increase the excretion of urine. The quantity of urine, therefore, that is eliminated in pathological renal conditions depends mainly upon these two sets of factors: first, the degree and the extent of the damage to the secreting cells, and secondly, the quantity and quality of blood which comes into contact with them. In widespread acute nephritis, the excretion of water is nearly always diminished, whereas in chronic diseases of the kidney, especially if these be of limited extent, the effects of the increased work of the

heart, the high blood-pressure and the well-maintained renal circulation predominate, such patients frequently secreting even more urine than does a normal individual. However, when cardiac failure appears, and the general blood-pressure falls, the amount of urine secreted by these patients is immediately diminished.

In diseases of the kidney, a diminution in the excretion of solids is often one of the earliest signs. The elimination of the various solids varies greatly and for reasons but little understood. The sodium chlorid usually follows the same law as the water; the phosphates, sulphates and nitrogenous compounds usually vary together; while the uric acid pursues its own independent course.

Albuminuria.—Although it has been generally considered that normal urine contains no albumin, recent work has rendered it very probable that traces of albumin, as well as of sugar, are normally present.[16] In order to demonstrate this trace of albumin, however, it is necessary to make use of special methods, such as the concentration of large quantities of urine. This albumin is believed by Senator and Mörner to be derived from the blood by a process of filtration through the glomeruli. Owing to the presence of chondroidin-sulphuric or nucleinic acids in the urine, this albumin may be precipitated by adding acetic acid. One should be cautious, therefore, and not conclude too hastily that the precipitate that so often results from the addition of acetic acid to urine is necessarily due to mucin or nucleo-albumin, derived from the cells of the kidneys or urinary passages.[17] The urine may, however, contain true mucin, which is free from phosphorus and which is derived from the epithelium of the urinary passages.[18]

There are persons who continually, or at intervals, show easily demonstrable quantities of albumin in their urine without feeling ill in any way. We cannot assume that the kidneys of such individuals are absolutely normal, in spite of the fact that the ordinary symptoms of chronic nephritis are absent and that the affected persons remain, so far as appearances are concerned, perfectly healthy. It is certain that chronic nephritis frequently follows quite a different course from that ordinarily described in our textbooks on medicine, and it is possible that many of these cases represent exceedingly mild forms of the disease.

Orthotic Albuminuria.—An albuminuria is of frequent occurrence in childhood and during the period of puberty, especially in delicate and anæmic individuals. Adolescence is probably a factor in some of these cases, for the condition often tends gradually to disappear after this period. Many of these individuals suggest a constitutional fault, and not a few improve as their general strength is built up. This type of albuminuria may also exhibit a tendency to occur in families. And finally, noxious influences of various kinds—for example, the infectious diseases—favor the onset of the condition.

Orthotic albuminuria is associated essentially with a change from the recumbent to the erect posture. It appears most readily in the morning after arising. If the individual remains upon his feet throughout the day, the albuminuria either disappears entirely, or is reduced to an insignificant amount. In many cases the diurnal variations show a definite cycle, *viz.*, a maximum secretion in the morning, a disappearance of albumin at noon and a secondary rise in the afternoon. Muscular exertion and cold baths tend to increase the albuminuria, and in some cases to precipitate it. Exercise is more potent in this respect in the morning hours. Excitement is another possible causative factor. Food taking is probably of little significance; in some cases, indeed, the albumin has been observed to disappear after eating.[19]

It is evident, therefore, that the occurrence of an orthotic albuminuria depends upon many and diverse factors. The conception that the condition is essentially due to circulatory disturbances accords well with the fact that a postural change is apparently the most important precipitating cause. The observations of Loeb[20] speak for this hypothesis. Jehle[21] has emphasized the importance of a lumbar lordosis as an etiologic factor and has shown that no albuminuria appears even in the erect posture if the lordosis be corrected. (Among other views as to the cause of orthotic albuminuria may be mentioned that of Teissier[22] who looks upon the condition as an evidence of latent tuberculosis, and that of Erlanger and Hooker[23] who emphasize as the pathogenetic moment a diminished pulse pressure in the glomeruli,

which leads to a retarded blood flow and possibly also to transitory injury of the vessel walls.—Ed.)

The proteids excreted by these patients have been shown beyond question to be the same as those normally present in the blood, *viz.*, albumin and globulin. In this respect, therefore, the albuminuria in the orthotic type does not differ from that present in nephritis. In other ways, however, the two conditions have nothing in common, even though the excretion of albumin in the nephritides may also be influenced by the bodily position. I have observed a number of such cases myself over a long period of years, and have never seen one go over into a true nephritis. Heubner[24] has had the opportunity of examining at autopsy a case of orthotic albuminuria (in which death was due to a cerebral embolism) and found the kidneys normal throughout.

Orthotic albuminuria may be cited as an example of a local circulatory disorder founded on the basis of a "constitutional weakness." The same type is predisposed during puberty to other local vascular disturbances, for example, syncopal attacks. In many individuals, however, exhibiting similar transitory albuminurias, no such constitutional fault is discernible.

The General Causes of Albuminuria.—The local disturbance in albuminuria we now know to be due to an abnormal permeability of the renal epithelium by reason of which the proteids of the blood are enabled to pass into the urine. This abnormal permeability must reside either in the renal cells themselves or in the basement membranes, for the walls of the capillaries will allow proteids to pass through normally. The epithelium of the glomeruli appears to be particularly susceptible to agents that increase the permeability in this manner;[25] whereas the cells of the convoluted tubules are thus affected only when the injurious agent is very powerful. It is difficult to judge, however, to what extent the latter have become permeable, for the coagulated proteids often seen in the lumina of these tubules must have come, in part at least, from the glomeruli above. *A priori* there is no evidence against the assumption that the tubular epithelium if injured can secrete albumin just as do other diseased parenchymatous cells.[26] As a matter of fact, this has been shown to occur in experimental toxic nephritis.[27]

We do not know the nature of the changes which render the

epithelial cells permeable for proteids. In many cases of albuminuria, no anatomical lesions of the kidney are demonstrable, while, on the other hand, granular and even fatty degeneration of the cells may be present, without any consequent albuminuria. Some have attached a certain significance to a loss of flagella from the cells of the convoluted tubules, yet it seems improbable that this should be of much importance, for these flagella may also be lost in conditions in which no albuminuria has been present. The more we attempt to correlate the grade of albuminuria with the extent of the anatomical involvement of the kidneys, the more forcibly will we be confronted with the meagreness of our knowledge of these conditions.

Albuminuria from Circulatory Disturbances of the Kidneys.—Circulatory disturbances of the kidneys may lead to changes in the epithelium and to albuminuria if the velocity of blood-flow through them sinks below a certain limit.[28] What this limit is, is not definitely known, though it seems to be different in different individuals. The retarded renal circulation may be due to a number of causes, such as obstruction of the renal veins, increase in the general venous pressure, spasm of the renal arteries from lead colic, tetanus, etc., or an increased pressure within the urinary passages, with secondary pressure upon the renal capillaries and veins. It seems probable that the retarded circulation primarily injures the renal cells, either by failing to supply them with sufficient food, or by failing to remove properly the waste products derived from their metabolic activities.

Toxic Albuminurias.—It is easy to conceive how poisonous substances circulating in the blood might injure the epithelial cells of the kidney and render them permeable to proteids. Such an effect may be produced by metallic poisons, by the balsams, etc., as well as by the more complex bacterial and other toxins. The various albuminurias that occur during the infectious diseases and those occurring during pregnancy belong, for the most part, in this category of toxic albuminurias. It is not a great step from these degenerative processes to the true renal inflammations. In the former only the parenchyma cells are affected, whereas in the latter the blood-vessels and the interstitial tissues are more or less diseased. Many poisons, in small doses, will produce degenerations, and in long-continued or very large doses, inflammations; whereas, others seem to cause an

inflammation from the start. Why some should thus affect the epithelium primarily and others the interstitial tissue is not known.

Schlayer and Hedinger[29] have distinguished two groups of toxic nephritides according to the functional disturbance present. In the first—of which cantharadin nephritis is an example—the renal vessels are primarily damaged, with the result that the secretion of urine is rapidly inhibited, though anatomical changes in the kidneys are slight or absent. In chromium nephritis, on the contrary, the tubules are the seat of the injury, the vessels at first being unaffected, and polyuria often being present. Yet despite the undoubted affinity of certain poisons for particular tissues, it is extremely difficult by elective poisoning to interfere merely with the function of the different types of cells.

The poisons that produce these toxic albuminurias are usually formed in the body during acute infectious processes; and, even in the so-called primary forms of nephritis, bacteria have been found in some instances in the urine, thus rendering it probable that the nephritis was of infectious origin. According to the opinion of experienced clinicians, nephritis may at times develop after exposure to cold, as from a severe wetting or from sleeping upon the ground, but as yet no adequate explanation has been offered of the manner in which such a nephritis is caused.[30]

The Varieties of Proteids in the Urine.—Most of the proteids that appear in the urine during renal diseases come from the blood-plasma, though as we have seen, a small quantity is possibly derived from the renal epithelial cells themselves. No definite ratio exists, however, between the amounts of albumin and globulin appearing in the urine.[31] Great importance was attached to this ratio when no distinction among the globulins was known. As a matter of fact the ratio between the albumin and the globulins, and between the two globulins (euglobulin and pseudoglobulin) varies considerably, and independently, it would seem, of the extent or type of the renal lesion, of the state of the circulation and of the individual's general condition.

Though the albumin and globulin of the blood include the greater part of the proteids appearing in the urine in the cases of disease of the secreting cells hitherto studied, this does not say that these are the only proteids that may appear under these con-

ditions. It is not impossible that in certain processes, the infectious diseases, for example, toxic albumin and globulins not identical with those of the blood, may arise and pass into the urine.

The Amount of Albumin Excreted.—The amount of albumin in the urine depends primarily upon the degree and extent of the injury to the secreting cells, and is largely independent of the quantity of urine excreted. In addition it seems to be influenced by the same factors which produce the so-called physiological albuminurias—posture, muscular exertion, etc.

Casts.—The diseased renal epithelium may become permeable to the red and white corpuscles of the blood, which can then pass into the urine. In addition to these blood-cells and the desquamated renal cells themselves, pathological urines often contain casts of the interiors of the uriniferous tubules. These casts are most frequently composed of a hyaline or granular material, but they may contain in addition various cells. The material composing them has been regarded by some authors as fibrin, parts of it often giving the Weigert reaction; yet it is questionable whether this hyaline material is true fibrin or not. Two theories as to the formation of casts have been advanced. According to the one, they result from the coagulation of the constituents of the blood that escape into the uriniferous tubules; while, according to the other and more acceptable theory, they are derived more directly from substances present in the renal cells, and are thus significant of the action of a noxious influence upon these cells.[32] Casts may be looked upon as the earliest evidence of an injury of the renal epithelium,[33] and as such they may appear in the urine even before albumin. In fact, the only relation existing between the appearance of casts and of albumin is that each is a sign of a damaged epithelium.

The Effect of Changes in the Composition of the Blood.—The amount of water in the body directly influences the secretion of urine, and it is well known, for example, that he who drinks much will also urinate much. Indeed, excessive drinking may be the primary cause of certain cases classified as diabetes insipidus, for it is possible to cure some of them merely by limiting the quantity of fluids taken by mouth. And the polyuria of certain cases of diabetes mellitus is of the same nature.

On the other hand, if the water in the body be diminished, either because the patient drinks little, or because he loses much water by other channels, the quantity of urine is correspondingly diminished. We see such a diminution after excessive sweating, especially in a dry climate, as well as in many diarrhœal disturbances, such as Asiatic cholera. The exact cause of the many variations in the amount of urine, which obviously serve to maintain a constant concentration of the blood, is not known.

Many solid substances also tend to increase the urinary secretion, among which are many of the constituents of normal urine. These bodies appear in the urine, not in proportion to their concentration in the blood, but depending upon whether their concentration in the blood is greater or less than normal. If present in greater amount than normal, they are rapidly excreted; if present in an amount less than normal, their excretion is greatly diminished. This depends upon the fact that the secreting cells have a different level of permeability for each of the substances under consideration. In this way the kidney tends to maintain the blood at a constant composition. And for this reason, also, the examination of the urine often furnishes the physician with valuable evidence as to the concentration of any particular substance in the blood. Careful and extensive metabolic studies are imperative in the particular case, however, because even normal individuals living under constant conditions may exhibit considerable and unexplainable variations in nitrogen and sodium chlorid elimination.[34]

When any solid is being excreted, it tends to carry a certain amount of water along with it into the urine. Advantage is taken of this fact in the use of certain substances as diuretics.[35] The bulk of the solid substances eliminated by the kidneys consists of waste products of digestion and of cellular metabolism. The most important of these have already been considered (see the chapter on Metabolism).

Special mention, however, must be made of the proteids. We have said that normal kidneys hold back these constituents of the blood plasma most carefully. This is not true, however, of all proteids that may happen to be present in the blood. Of the many that have been artificially introduced into the circulation a small number, such as egg albumin, casein and hæmo-

globin, immediately pass through into the urine.[36] Even when uncoagulated egg albumin is taken by mouth in large quantities, some will often be excreted by the kidneys. Now, abnormal proteids are undoubtedly formed in the body during some pathological processes, and especially during the infectious diseases, and it seems not improbable that many of the albuminurias present in these conditions are due, not to a primary injury to the renal structures, but to the elimination of abnormal proteids that cannot be assimilated in the body. So, too, those proteids sometimes found in the urine during leukæmia, and which are precipitated by the addition of acetic acid, are also possibly excreted because they cannot be assimilated. In fact, such abnormal proteids have been demonstrated in the blood itself.

Albumoses and peptones will also appear in the urine if they be injected into the circulation in sufficiently large quantities. They do not appear normally during digestion, apparently because they undergo a further cleavage in the intestines. Possibly this splitting process does not take place under certain pathological conditions and this may explain the albumosurias occasionally seen in connection with ulcerations of the intestinal wall.[37] In other conditions, as in fever, albumoses are formed during a pathological destruction of the proteids of the body, and here again they may appear in the urine.

Living bacteria may be excreted by the apparently intact kidneys, and so reach the urine. They can undoubtedly pass through the glomeruli in this manner, for micro-organisms have been seen within these structures.

The Localization of Functional Disturbances.—For a proper appreciation of pathological alterations in renal function, we must have clearly in mind the mechanism of elimination under normal conditions.[38] Physiologists are for the most part agreed that the excretion of different substances is carried out by particular elements of the renal tissue. Thus to the glomeruli, primarily, is generally accredited the elimination of water,[39] though this function may in turn be affected by the condition of the circulation in the tubules. Yet the factors underlying the excretion of water—to some of which we have made reference in the preceding paragraphs—are apparently far from simple. Indeed, capable observers[40] have attributed to the tubules the task of eliminating the water. Further-

more, the amount of water excreted is assuredly dependent upon the sodium chlorid elimination.[41]

An extensive literature has developed along the line of functional disturbances in diseased kidneys. In a way, the more recent studies are as ambiguous as the older ones. The problem is indeed a difficult one, for, as a rule, the nephritides do not involve a particular structure, but are diffuse, while the tissues that remain free not only functionate as before, but may become compensatorily active. These various considerations must not be lost sight of in the interpretation of the different functional disorders. Important strides have been made, however, in the classification of the nephritides according to the disturbance of function present.[42] Thus, in some cases, the elimination of urea may be interfered with, while that of sodium chlorid is normal, and vice versa. A disturbed urea and lactose elimination is attributed by many to a functional disorder of the glomeruli, while a failure to excrete salt is looked upon as evidence of an injured tubular epithelium. Observers are not lacking, however, who have different views as to the elimination of urea and sodium chlorid; and the old conception of Ludwig, *i.e.*, that the excretion of water and of crystalloids takes place by a process of filtration in the glomeruli, has once more been revived.

It may easily occur, therefore, that a diseased kidney is no longer capable of maintaining the normal composition of the blood. The acutely inflamed organ is appreciably less efficient than the normal one.[43] The most diverse types of anatomical change may be responsible for these functional disturbances. The present lack of harmony between clinical and autopsy findings in cases of nephritides is familiar to all of us. A high degree of functional insufficiency may arise with apparently insignificant anatomical changes, a phenomenon which Schlayer has also observed in experimental nephritis.

The Effect of Disturbances of the Urinary Secretion upon the Body.—Diseases of the kidneys may affect the body in at least two ways—either by allowing substances to pass out which ought to be retained, or by retaining substances which ought to pass out. Of the substances that escape abnormally, albumin is the only one of importance. (Sugar appears in the urine in abnormal

amount for a different reason, *viz.*, because its concentration in the diabetic blood is increased.) The actual loss of proteids by this channel is, however, relatively slight, amounting to only a small number of grams a day. It seems quite improbable that this small loss should in itself produce much effect upon the body as a whole, though it cannot be denied that it may affect the composition of the blood to some extent (see p. 140).

On the other hand, the retention of substances in the body that should normally be excreted apparently leads to a variety of disturbances, among them œdema, arterial hypertension and uræmia.

Uræmia.—Not infrequently, during the course of renal disease, a group of symptoms develops which seems to be caused by some sort of intoxication. This is called uræmia,[44] and it presents the most varied clinical picture. The patient may become apathetic or comatose, or, on the contrary, extremely irritable. He may have local or general convulsions, or suffer from paralyses of various parts of his body. Sometimes he becomes blind, though the eyes are objectively normal. The heart's action is at first slow and irregular, but later very rapid; the respirations become deeper or assume the Cheyne-Stokes type; finally there may be vomiting and diarrhœa. These are the most important symptoms of this condition. They occur singly or in groups, and they may develop suddenly or slowly. The greater number of them is evidently due to cerebral disturbances, probably to changes in the nerve cells similar to those seen in botulism and in mushroom poisoning.

It has recently been urged that these many and varied symptoms do not all arise from a common cause, a view with which I am inclined to agree. Yet it is difficult to decide this question, for, as is well known, the same poison may act quite differently upon different individuals, and upon different organs in different patients, owing to individual variations in susceptibility. As we shall see, furthermore, there are reasons for believing that a number of causes may be operative in the production of uræmia.

Beyond doubt, the symptoms of uræmia are caused by some sort of poisoning, and our first supposition would naturally be that this intoxication is due to the retention of substances in the body that should normally be excreted by the kidneys. As a matter of fact, patients in uræmia frequently excrete abnormally small amounts of urine

and of urinary solids, particularly those of a nitrogenous character.[45] Indeed, the excretion of various solids may be diminished even though the quantity of urine be increased. This latter fact has been advanced as an argument against the toxæmic nature of uræmia. The point is not well taken, however, for if the onset of uræmic manifestations happens to coincide with the resorption of œdematous fluids—and hence with an increased output of urine—we may properly assume that poisons which have accumulated in the tissues are then washed into the circulation and are thus enabled to exert their toxic action.

The retention of urinary substances in the body has, furthermore, been directly demonstrated by examinations of the blood. The number of molecules in the plasma is increased during uræmia, for its freezing point is lowered. Since its electrical conductivity is unaltered, however, the increased concentration of the blood cannot be due to an excess of electrolytes, such as salts, but must be laid to an excess of organic molecules of some sort.[46] Chemical examinations have shown that these are mostly organic nitrogenous compounds that have resulted from proteid decomposition, and constituting the so-called residual or non-coagulable nitrogen.

Recent literature contains many studies indicating the importance of the non-coagulable or non-protein nitrogen element in the production of uræmia and in renal insufficiency in general.[47] The retention of these bodies is greatest in cases of contracted kidney which are on the verge of uræmia;[48] while in the other forms of nephritis the amount is considerably less. Though urea is included in this residual nitrogen, we can readily eliminate it as a factor in the production of uræmia, for, as we shall at once see, it is non-toxic. Hence, for the non-coagulable nitrogen to be of significance in uræmia, it must contain poisonous products of proteid metabolism. Soetbeer,[49] in fact, has shown that in nephrectomized animals these toxic albuminous substances are present most abundantly in the blood, and to a less extent in the brain and other organs.

(The efforts to localize the disturbance of renal function by the ability of the kidneys to excrete certain substances introduced into the circulation (see p. 427) have not met with a very great success. This has been due to the fact already alluded to that anatomical changes in the organs—except possibly in acute cases

—are ordinarily not confined to a single structure but tend to be more or less diffuse. For this reason, attention has been focused more recently upon the concentration in the blood of the non-protein nitrogen as an index of the functional efficiency of the kidneys, particularly in view of the fact that the quantitative methods of determination have been greatly simplified.[50] In general, observers are agreed that the degree of retention of these bodies is of value both in a diagnostic and prognostic way.[51] Attention has already been directed to those cases of arterial hypertension without apparent renal involvement in which the estimation of the non-coagulable nitrogen may speak unequivocably for a nephritis (p. 81).

It has been asserted further that another and simpler functional test parallels so closely the residual nitrogen determination as to be available for routine work. This is the phenol-sulphonphthalein test of Rowntree and Geraghty. The considerable literature devoted to this point is in general confirmatory.[52]—ED.)

A number of facts speak against the view that uræmia is caused by the retention of substances that are normally excreted through the kidneys In the first place, an absolute anuria may persist for days, without producing uræmic symptoms, and, furthermore, even though death results from suppression of urine, the associated symptoms do not precisely coincide with those of uræmia. Patients with anuria seem to pass gradually into coma without any irritative cerebral symptoms, and the uræmic hypertension, bradycardia and convulsions are generally absent. Furthermore, experimental ligation of both ureters is better borne than is extirpation of the kidneys.

No well-defined substance has yet been found that is both retained in the body during uræmia and is capable of producing uræmic symptoms when injected into a normal animal. Many such substances have been described, yet not one has stood the test of time. Urea, for example, is retained in the body during uræmia, yet it is not toxic in these amounts,[53] and a similar retention may continue for days without the appearance of uræmic symptoms. Some have regarded the potassium salts as toxic agents, yet the quantity of these salts in the blood of uræmic dogs was not found to be increased. The evidence regarding creatin and uric acid in their

relation to uræmia is likewise very inconclusive. Yet, despite the apparent non-relationship to uræmia of these various nitrogenous bodies, as individuals, there is little doubt that a retention of nitrogenous substances in the aggregate plays an important part in the condition (p. 431).

The urine even in health, however, possesses certain toxic properties, the exact cause of which is at present unknown,[54] Its poisonous action is frequently increased in disease, and it is quite possible that in nephritis toxic substances are formed in abnormally large quantities, and that they are not eliminated properly by the kidneys. Yet this is a pure hypothesis built upon a very insecure foundation, for but little reliance can be placed upon inferences as to the toxicity of normal and pathological urines, when the inferences are derived from the effects of injections of the whole urine into animals. Until some definite toxic substance can be isolated, this hypothesis will continue to retain a more or less questionable standing.

Finally, there exists the possibility that uræmia is due not to a failure on the part of the kidney to eliminate poisonous substances from the body, but to a pathological alteration in some of its metabolic functions. Of these functions, we know comparatively little; yet that the kidney does possess such functions is proved by the well-known fact that the renal cells can form hippuric acid out of benzoic acid and glycocoll. Brown-Séquard[55] has elaborated the theory that the kidney furnishes an internal secretion to the body, and he has attempted to explain uræmia from this standpoint. Various effects are said to follow the injection of renal extracts, and it has been found that substances tending to raise the blood-pressure are present in normal kidneys, and that they are present in especially large quantities in pathological kidneys[56] (but see p. 339). The theory of Ascoli[57] that nephrolysins are of importance in the production of uræmia has not been confirmed.[58] Possibly, further work along these suggestive lines will aid us in our understanding of uræmia.

In conclusion, we may say that although a complete suppression of urine is fatal, the symptoms produced are not absolutely identical with those of uræmia. The convulsions, the increased blood-pressure and the slow pulse—all of which occur so frequently in uræmia—are in all probability caused not by the reten-

tion of normal urinary products but by some special uræmic toxin. This hypothetical toxin acts especially upon the central nervous system, and here more particularly upon the cerebral cortex and the medullary centres. In either place it may produce a stimulation or a paralysis.[59]

The Urinary Passages

Any portion of the urinary passage from the kidney to the mouth of the urethra may be diseased. Affections of the urinary bladder and of the renal pelves stand in close etiological relation to one another. If, for example, one of the latter is inflamed, the infected urine that flows into the bladder may there cause changes. On the other hand, if the former be the seat of an inflammation, this may easily spread upward through the ureters to the pelves of the kidneys. Pyelitis is most frequently caused by just such an ascending infection, and every long-continued cystitis is a menace to the patient, for it may produce an inflammation of the renal pelvis or of the kidney itself. Certain infections, especially tuberculosis, affect the renal pelvis primarily, in which case the process enters through the kidneys.

Pathological conditions of the urinary bladder may be caused by vesical calculi, by the irritative or infectious character of the urine that comes from the kidneys or by inflammations in the neighborhood that extend into it by contiguity. More frequently, however, the infectious agent reaches the bladder through the urethra. It is possible that in some instances bacteria enter from the anterior urethra, because the sphincters are weakened or paralyzed; but as a rule the micro-organisms are directly introduced by a catheter or some other instrument. Such an introduction of bacteria into the bladder does not necessarily cause an inflammation, for the normal, complete evacuation of this organ protects it to a certain extent against infection. On the other hand, infection is greatly favored by stasis of the urine, and for this reason prostatic hypertrophy, urethral strictures, vesical calculi, tumors, etc., are frequently followed by cystitis.

When bacteria develop in the stagnating contents of the bladder they may cause various urinary decompositions. Of these none is more frequent than the so-called ammoniacal

decomposition, in which a portion of the urea is transformed into ammonium carbonate, and which may be brought about by various bacteria. In other forms of urinary decomposition the neutral sulphur in the urine is converted into hydrogen sulphid. The effects of such fermentations are both general and local. The ammonium salts and the hydrogen sulphid may be absorbed through the altered vesical mucous membrane and produce their general toxic effects. In addition to this, the ammonia directly attacks the bladder mucosa.

Urinary Calculi.—Urinary calculi[60] may be composed of various materials, such as uric acid, the urates, calcium oxalate, cystin, the carbonates and phosphates of the alkaline earths, etc. In addition to one or more of these, the calculus always contains a framework of a proteid-like substance, and this is often so intimately mixed with the salts present that chemical methods are necessary to distinguish them. In some cases the proteid element is so pronounced that we speak of proteid stones.[61] Some stones are of uniform structure throughout, while others show a more or less concentric arrangement, owing to the fact that layers of one substance alternate with layers of another.

An organic framework is present not alone in formed urinary calculi, but in urinary crystals of every description.[62] This fact is of considerable theoretical interest; and whereas it was formerly supposed that the organic framework was pathological, and was a necessary condition for the formation of calculi, it is now regarded as a physiological structure and comparatively harmless. The material out of which this framework is composed is apparently present in every urine, and is precipitated along with the inorganic salts. No special explanation, therefore, of the presence of this organic framework in urinary calculi would seem to be necessary.

Ebstein,[63] however, has expressed the opinion that the organic framework of the crystals is quite different from that of the renal calculi. The framework of the latter, in his opinion, is formed only when, under pathological conditions, an abundance of proteid material arises in the urinary passages. The albumin and mucin normally present in the urine are not adequate for this purpose. In my opinion, the problem is satisfactorily solved on the basis that the salts, when precipitated, carry proteid material with them, just as other minerals are able to take up proteid

substances. This calculous proteid framework varies with the composition of the urine. It is always secondary, however, to the precipitation of the stone-forming salts.

The calculi most frequently found in the bladder are composed of uric acid or of the urates. Uric acid stones are often formed in the kidneys themselves and apparently even during the earliest periods of life. As is well known, uric acid deposits are frequently present in the uriniferous tubules of the fœtus and of the new-born infant, forming the so-called uric acid infarcts. For our present purposes, it is immaterial whether the uric acid in these cases is excreted in excessive amounts, or whether it is merely precipitated with unusual ease; for the formation of calculi depends primarily upon the precipitation of salts. Apparently these renal deposits in new-born infants are normally washed out of the kidneys and out of the urinary passages without causing any symptoms. Possibly, however, the infarcts stand in some close causal relation to the formation of uric acid stones in childhood.

Since the formation of these calculi depends primarily upon the precipitation of the uric acid out of the urine, two factors are of importance in this respect, first, the amount of uric acid secreted, and secondly, the ability of the urine to hold this in solution. Of these, the latter is the more important and the more variable. Urine dissolves far more uric acid than does pure water.[64] Normally, the uric acid is present in the urine mainly as a mono-sodium salt. The mono-sodium phosphate of the urine, however, tends to take the sodium away from the mono-urate, forming a di-sodium phosphate and leaving free uric acid, which is comparatively insoluble. The presence of free carbonic acid in the urine tends to hold uric acid in solution.[65] It is, furthermore, quite possible that uric acid is often held in solution in the urine as some special combination. We know, for example, that the quantity of urea in the urine affects the solubility of uric acid, and it is probable that other organic substances will do the same. Uric acid calculi are often associated with gout, the two being grouped together under the name of the uric acid diathesis. We have already seen that the uric acid within the body is probably held in solution in organic combinations (*cf.* p. 368), and the same may be equally true concerning the urine. We may say, therefore, that the precipi-

tation of uric acid out of the urine depends upon numerous factors and that the presence or absence of other substances probably plays a more important rôle than does the mere quantity of the acid itself. The more important and difficult element of the problem, however, is the determination of the mode of formation of the primary nucleus. When the latter is once present, the calculus will arise in due time by the precipitation of uric acid from normal urine.

The mode of origin of oxalate calculi is not better understood. The solution of calcium oxalate in the urine is greatly favored by an acid reaction. If this latter be reduced from any cause, the mono-sodium phosphate tends to be converted into di-sodium phosphate, and the precipitation of calcium oxalate is favored; yet this appears to be only one factor in the process.[66]

The phosphates of the alkaline earths are soluble in the urine mainly as mono- or di-phosphatic salts, and they tend to be precipitated when the reaction of the urine becomes alkaline and normal phosphates are formed. Ammonium-magnesium phosphate is also formed under these circumstances.

These phosphatic calculi are formed almost exclusively in the bladder, but they frequently precipitate about a nucleus composed of some other material, such as a uric acid stone or some foreign body that has been artificially introduced into the bladder. Their formation is greatly favored by stagnation of urine, and, as a consequence, they occur most frequently in association with cystitis; for this, as we have shown, is itself favored by stagnation, and is frequently accompanied by an alkaline reaction of the urine, owing to the associated ammoniacal fermentation. To stagnation, also, is probably due the formation of calculi in individuals with cord lesions.

In the condition known as phosphaturia, calculus formation does not take place, though the phosphates are present in the urine in sufficient amount to render it cloudy, either when passed or shortly afterward. These phosphatic precipitates, which are made up chiefly of calcium and magnesium phosphate and carbonate, appear when the diet is rich in alkalies or when there has been a loss of acid from the body, as is seen for example in gastric hyperacidity. Though the causes of phosphaturia are generally unknown, it is a fact that the condition is often seen in young individuals of a nervous constitu-

tion.[67] The French, indeed, speak of a phosphatic diabetes and see in the condition a pronounced nervous element. Why, in phosphaturia, there occurs an increased elimination of calcium salts through the urine at the expense of the usual intestinal excretion is not definitely understood. Soetbeer has suggested the presence of a colitis as the cause of this lessened intestinal elimination, but this has been disputed.

Cystin and xanthin calculi are extremely rare. The former is a substance containing sulphur, and is derived from proteid sources. It appears to result from an inability on the part of the body to complete the destruction of the sulphur-containing portion of the proteid molecule (p. 336). Apparently, it never occurs in normal urine. Xanthin is present even in normal urine in small amounts, but the cause of its precipitation is not understood.

The Symptoms of Urinary Calculi.—The hard, uneven stones, especially the uric acid or calcium oxalate calculi, irritate the mucous membrane of the urinary tract and cause inflammations, pain and hemorrhages. If the calculus obstruct a ureter, attacks of renal colic, with severe pain and vomiting, may follow. If the occlusion persists for a long period of time, hydronephrosis and the other sequelæ of urinary retention are likely to develop.

Vesical calculi may suddenly stop the flow of urine by dropping before the mouth of the urethra. This gives rise to vesical tenesmus, which is not, however, a pathognomonic symptom of calculi, but may be produced by inflammations of the neck of the bladder, by vesical tumors or even by a highly concentrated urine. The symptoms of vesical tenesmus are very similar to those of tenesmus of the rectum. The irritation of the neck of the bladder causes a frequent desire to urinate, and the bladder consequently contracts frequently and forcibly, causing considerable pain; yet, on account of the small amount of urine present, but little can be voided.

The Origin of Pain in the Urinary Passages.—A diseased kidney may cause pain, or at any rate, a dull feeling of pressure in the lumbar region. This is not infrequently observed in association with acute or chronic nephritis. More severe pains are usually due to affections of the lower urinary passages, and they, as a rule, are caused by a spasm of the smooth muscle

lining the urinary tract. These spasms are caused by reflexes from the mucous membrane, which originate either from the irritation produced by a foreign body, or from inflammatory or ulcerative processes in the mucous membrane itself. The muscular spasm in these cases is comparable to that which gives rise to biliary or intestinal colic. Apparently the mucous membrane possesses nerves of sensation, the direct irritation of which may also cause pain.

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[62] Moritz: Kongr. f. inn. Med., 1896, 523.
[63] Ebstein: Deutsch. med. Wochenschft., 1908, No. 32.
[64] Bunge: Physiol. Chem., 3rd edit., 308.
[65] Klemperer: Zeitschft. f. physikal. Therapie., iv, 48.
[66] Klemperer: Berl. klin. Wochenschft., 1901, 1289; Klemperer and Tritschler, Zeitschft. f. klin. Med., xliv, 337.
[67] See Soetbeer: Jahrb. f. Kinderheilk, lvi, i; Soetbeer and Krieger, Arch. f. klin. Med., lxxii, 553; Langstein, Medizin. Klinik, 1906, No. 16, Klemperer, Therap. d. Gegenwart, 1908.

CHAPTER XII

THE NERVOUS SYSTEM

THE activities of the nervous system give rise to two classes of phenomena—those pertaining to the body and those pertaining to the mind. We do not purpose considering the latter, nor even discussing the relationship that exists between the body and the mind. In the present chapter, we plan to limit our discussion, in a general way, to those disturbances of the nervous system which do not affect the mind, even though this division is an artificial one and cannot be carried out strictly and consistently.

The nervous symptoms that we shall consider may be divided into two main groups. Those in the first group are called *focal symptoms*, because they are caused by pathological changes involving certain limited portions of the nervous system. Those in the second group are termed *general symptoms*, because the agent that causes them affects the nervous system as a whole. Of these general symptoms, some evidently proceed from certain definite localities; while the origin of many others cannot be traced. The same general injurious agent may act upon all parts of the nervous system, yet it affects certain portions more than others, because the former happen to be more vulnerable to the particular agent in question.

Disturbances of the Circulation.—The central nervous system must receive a sufficient supply of blood in order to functionate properly. Some of the symptoms that result from circulatory disturbances have already been mentioned in the chapter on respiration. We spoke there of the extraordinary *sensitiveness of the respiratory centre to any change in the quantity or quality of the blood* that comes to it, as well as of the effects of such changes upon other medullary centres. The cerebral cortex is not affected until some time after the medulla, at which time the consciousness becomes clouded and the horrible sense of suffocation is diminished or lost. Although the brain is ordinarily extremely sensitive to circulatory changes, it often appears as if it can accommodate itself to an insufficient blood supply in chronic circulatory derangements. It is extremely difficult, however, to form an accurate judgment on

this question, for we have no method of measuring the circulatory disturbances in the brain; yet it is often truly astonishing to see what little effect the most pronounced chronic venous stasis or the most marked arterial anæmia produce upon the cerebral functions.

The temporary loss of consciousness known as *fainting* is usually due to an acute cerebral anæmia. It may occur in strong and healthy individuals, but it is much more frequent in anæmic girls or in older individuals with degeneration of the cerebral arteries. During the fainting spell the patient loses consciousness, falls and lies for a time, breathing quietly, but with a pale, non-cyanosed face. Finally, after a while, he gradually recovers. Although the cerebrum has ceased to act, the medulla appears to perform its functions quite normally, just as it does during light narcosis. It seems improbable, therefore, that the disturbance of circulation in fainting affects all parts of the brain equally; for if this were so, we should expect medullary symptoms. We know that localized anæmias frequently occur in other parts of the body, and that in arteriosclerosis such circumscribed circulatory derangements are particularly frequent; and it seems quite possible that the anæmia causing the syncope affects only a part of the brain, as might happen, for example, if certain vessels became narrowed either by a spasm or by a relative thickening of their walls.

Other anæmic manifestations of nervous origin are more difficult to explain. Some, such as headache, ringing in the ears, spots before the eyes and dizziness, appear to be *irritative* in character; while others, such as the common feeling of lassitude, are *depressive*. These symptoms are generally ascribed to a cerebral anæmia which either diminishes the oxygen supply to the brain or affects its nutrition in some other way; but these suppositions have not yet been definitely proved. There are many other possibilities. Chemical substances, resulting from pathological alterations of the general metabolism, may poison the brain in some manner; and it is even possible that the symptoms do not originate in the brain at all, but in the peripheral sense organs. Finally, Lenhartz [1] has shown that the headache and dizziness of chlorosis may be associated with an increase in the subarachnoid pressure.

The Cerebrospinal Lymphatic System.—The brain and spinal cord are suspended in a fluid that is constantly changing through

the processes of secretion and absorption. We need not describe the many advantages of this mechanism; how it acts as a cushion about the delicate nervous structures when the body is jarred, nor how the brain is protected from rapid alterations in arterial pressure by the layer of lymphatic fluid that encircles each of its blood-vessels.

Most observers have found the pressure of the cerebrospinal fluid to be normally rather low, although it apparently varies considerably in different individuals.[2] Its height depends in part upon the general blood-pressure, but mainly upon the relation that exists between the secretion and the absorption of the lymph. The characteristic composition of the cerebrospinal fluid—*viz.*, a low percentage of albumin and a high percentage of potassium salts—shows that it is not an ordinary transudate, but a secretory product from certain cells, probably those of the choroid plexuses.[3] The resorption[4] of this fluid takes place mainly in the Pacchionian corpuscles and to a lesser extent in the lymphatics of the nose and neck.[5]

Increased Cerebral Pressure.—The pressure of the cerebrospinal fluid may be pathologically increased to varying degrees and by different causes.[6] For example, tumors may bring this about merely because they take up space within the cranial cavity, though they are especially liable to do so when they press upon the veins of Galen and thus impede the outflow of venous blood. Intracranial hemorrhages may also increase the cerebrospinal pressure.

If the cranial cavity becomes crowded from any cause, the brain substance cannot be compressed into a smaller space, for the nervous tissue is practically incompressible.[7] A certain relief is afforded, however, by the escape of cerebrospinal fluid into those portions of the dura mater that are comparatively distensible, such as is the dura of the cord. A new equilibrium of pressure is then established. What the new pressure will be depends upon the size of the compressing agent, the distensibility of the dura and, finally, upon the relation that exists between the secretion and absorption of cerebrospinal fluid. It is apparent that when so many factors enter into the final result the same cause may produce quite different effects in different individuals.

From these considerations it would appear that when a

hard body is added to the contents of the skull the increase in pressure would be roughly proportionate to the size of the "foreign body," and that the space taken up by smaller bodies could be fairly well compensated for by the escape of lymph from the cranial cavity.[8] In some cases, however, especially in certain brain tumors,[9] no such definite relation seems to exist between the size of the tumor and the increase in the cerebrospinal pressure. The smallest tumor may cause a tremendous rise in pressure. Furthermore, if some of the cerebrospinal fluid be drawn off in order to relieve the pressure, it will frequently re-collect with great rapidity. These facts do not accord with the view that brain tumors increase the cerebral pressure solely by their mechanical action. It would seem rather as if the production or the absorption of the cerebrospinal fluid were directly affected. Possibly the conditions present are analogous to those that exist in tumors of the pleura or of the peritoneum, *i.e.*, some sort of an inflammatory process is taking place in the arachnoid.[10] In favor of this view are the facts that the cerebrospinal fluid of these patients often contains more albumin than normally,[11] and that the accompanying choked disk is almost certainly of an inflammatory nature.

The increased cerebral pressure that accompanies meningitis is caused by a disturbance in the balance between the production and absorption of cerebrospinal fluid. It seems probable, indeed, that both the production is increased and the absorption diminished in this condition.

The chronic hydrocephalus of children is characterized by a large collection of cerebrospinal fluid, but its cause is not well understood. Perhaps a mild inflammatory process is present (ependymitis), though this seems improbable in most cases, from the fact that the percentage of albumin in the fluid is not increased. Chlorotic girls frequently show an increased cerebral pressure, yet here again the cause is very uncertain. The mild optic neuritis often seen in these patients may possibly be produced by the increased cerebral pressure, though it seems more probable that it results directly from the poor nutrition of the optic nerve. That the headache accompanying cases of arterial hypertension (nephritis, arteriosclerosis) is often the result of an increased cerebral pressure is

evidenced by the benefit seen in many instances after a lumbar puncture.

When the pressure of the cerebrospinal fluid is increased from any of these causes, certain symptoms usually follow, among which are headache, general bodily and psychic weakness, and characteristic alterations in the ocular fundi—the so-called choked disks. These have been termed the symptoms of latent cerebral pressure, and they are supposed to be caused by the tissue changes that follow the increased pressure in the cranial cavity. Possibly they depend less upon the height than upon the duration of the increased pressure.[12] It would be interesting to know what the minimum pressure is that can produce a choked disk, but the data at our disposal do not suffice to determine this.[13] And it may be that the individual variations are so considerable that no definite minimum can be fixed.

Although choked disk is one of the most important clinical signs of increased cerebral pressure, the manner in which it is produced is still very uncertain.[14] According to the opinion of most ophthalmologists, a mere increase in the intracranial pressure does not suffice to cause it, and other factors must be present. Anatomically, it usually appears to be a true inflammation, involving both the nerve and the neighboring retina. The optic papilla is swollen, and there is an associated œdema and venous stasis, but we do not know whether the œdema and stasis ordinarily develop before the inflammation or not. That stasis alone should cause the inflammation is contrary to all our pathological experience with œdema in other parts of the body. It is quite possible that some inflammatory irritant, produced by the changes within the brain, acts upon the retina. According to this view, two factors contribute to the causation of choked disk: first, an increase in the pressure of the fluid within the optic sheath; and secondly, some unknown inflammatory agent. This hypothesis would explain many peculiar cases in which a choked disk is absent even though the intracranial pressure is high, as happens in some cases of hydrocephalus; here it would appear that the inflammatory factor is absent. On the other hand, in intracranial conditions of slow development, such as in certain abscesses and tumors, choked disk is often absent because there is no increase in intracranial tension.

If the pressure of the cerebrospinal fluid be still further increased, a second series of phenomena develop, the so-called direct, or manifest, symptoms of cerebral pressure. The essential cause of these is a disturbance of the cerebral circulation. We have already described the peculiar conditions that govern the intracranial pressure and how space may be made for foreign bodies by an escape of lymph. When, in spite of this compensatory mechanism, the pressure attains a certain height, those parts of the vascular system that can be compressed most easily—*i.e.*, the veins just before their entrance into the rigid sinuses—become narrowed or even closed. The resulting stasis of blood increases the pressure in the corresponding capillaries and the veins are then opened again, so that they alternately open and close, or, as Grashey says, they vibrate.[15] It is not certain what cerebral manifestations accompany this phenomenon. From experimental data, it would appear that the really characteristic symptoms of cerebral compression only begin at about the time when the intracranial pressure becomes sufficient to compress the arteries. It is then that we have the characteristic stupor, the vomiting, the slowing of the pulse and the respirations, and finally the general epileptiform convulsions. The primary cause of these symptoms seems to be an arterial anæmia that occurs because the subarachnoid pressure is greater than the arterial pressure. It is theoretically possible, therefore, that these symptoms could be produced either by a rise in the subarachnoid pressure or by a fall in the arterial pressure. When the nervous symptoms of increased cerebral pressure have once become established, they may continue for some time, even though the intracranial pressure lessens, for the reason that less force is required to hold the vessels closed than to compress them originally.

The absolute amount of cerebral pressure necessary to produce these direct symptoms is, therefore, rather indefinite, and it often happens that during the course of indirect symptoms, the direct ones will appear and again disappear, apparently on account of circulatory disturbances.

According to Cushing, a continuation of life after compression of the cerebral arteries has once taken place, is made possible only by an increase in arterial pressure. The latter is

brought about by a stimulation of the vasomotor centre as a result of the anæmia. To what extent these experimental observations relative to the interaction of the intracranial tension and the cerebral circulation are pertinent to conditions in man, is still undetermined. So far as I know no observations have been made which bear upon such variations in blood-pressure consequent to an increased intracranial pressure. (A rise of blood-pressure after cerebral hemorrhages in man has been demonstrated, the extent of the rise being looked upon as an index of the amount of compression exerted upon the medulla.[16]—Ed.)

The recent tendency, it would seem, has been to emphasize the circulatory basis of the manifestations of increased intracranial pressure, thereby underestimating the importance of changes in the brain substance itself as the cause. Symptoms of increased pressure may appear even in the absence of a cerebral anæmia, indeed even when the indications are that the arteries are well filled. Too little importance has been attached to the important, if not predominant, rôle played by compression, distortion and displacement of the cerebral tissue itself.

Cerebral Concussion.—The symptoms of cerebral concussion differ considerably from those of compression. The pale, unconscious patient lies with relaxed muscles and with weak respirations. His pulse is soft and small, its rate being either increased or diminished. His pupils are often immobile; and vomiting frequently occurs. Indeed, he might be thought to be suffering from a fainting spell.

Cerebral concussion is ordinarily produced by a violent blow upon the head or upon some other part of the body, yet no definite relation seems to exist between the force of the blow and the severity of the symptoms, and even serious cerebral injuries due to violence may be unaccompanied by any of the typical manifestations. The symptoms of concussion are essentially those of cerebral inactivity, reaching different grades in different cases. In the milder form of concussion, the cerebral cortex alone is affected (unconsciousness), in the more severe forms the medullary centres become involved (respiratory and circulatory disturbances), while, in the most severe, the vital functions are suspended.

No definite anatomical changes in the brain,

common to all cases of concussion, have been found.[17] The symptoms can hardly be due to circulatory disturbances, for they have been produced on bloodless frogs. It seems quite probable that they are caused by injuries to the finer connections between the nerve-cells in the brain; and we know that very severe concussions may even produce slight but demonstrable lesions in the central nervous system.

Kocher has called attention to the fact that cerebral concussion, so-called, is hardly of uniform etiology. He has suggested as a more suitable term, acute brain compression (Hirnpressung), the chief manifestations in the process being, in his opinion, the phenomena of acute compression, and the consequent lesions of the nervous tissue. I am likewise of the opinion that we must be reserved in our interpretation of cerebral concussion, both because of the poorly defined clinical picture, which may closely resemble conditions due to definite anatomical lesions, and also because of our inability to produce in animals an exact replica of the picture in man.

Cerebral Hemorrhage and Embolism.—Closely related to the manifestations of increased intracranial pressure are those associated with disturbances in the cerebral arteries, and known as cerebral insult. Apoplexy is generally due to alterations in the vessel walls—the so-called miliary aneurisms. The latter, under the influence of an augmented blood-pressure, or even with a normal tension, rupture and permit of an escape of blood into the surrounding tissues. The extent of the hemorrhage and its rapidity of formation depend upon the size of the vessel and of the opening in its wall. The severity of the picture varies with the increase in intracranial pressure and with the amount of the extravasation. There is ordinarily a loss of consciousness and a slowing of the pulse and respirations. The early fall in temperature is succeeded by a rise. Death often occurs without a return of consciousness.

These symptoms are the direct result of the cerebral trauma, consequent to the extravasation of blood; added to the extensive destruction of brain-tissue is the damage wrought by the increase in intracranial tension. In other cases, the insult is gradual in nature, probably because only a small amount of blood escapes at one time, in which event the actual destruction of tissue is slight and the increase in tension is slow and limited. In those

cases in which the insult is entirely absent, the hemorrhage has been small and gradual, and the tissue destruction and increase in tension insignificant, for here the cerebrospinal fluid has had time to distribute itself elsewhere. As the vessels of the cortex are smaller, and exhibit a lower pressure than do those of the base, a rupture of the former is attended with less pronounced insult manifestations.

The symptoms consequent upon a sudden closure of a cerebral vessel are so similar to those associated with a hemorrhage as often to be indistinguishable from them. As Marchand has pointed out, the closure of a cerebral artery is quickly followed by a stasis in the neighboring capillaries and veins. The anæmia of certain parts of the brain thereby produced, accounts in all likelihood for the loss of consciousness. The next stage is one of cerebral œdema, to which are due the symptoms of increased pressure. The focal symptoms accompanying hemorrhage and embolism depend upon the location of the tissue injury, just as is the case with tumors.

Disturbances of Motility.—The direct motor impulses travel from the cerebrum to the muscles through two sets of fibres. Of these, the first begins in the ganglion cells of the cortical motor area and pass by way of the pyramidal tracts to the anterior horn cells of the spinal cord, or to the corresponding nuclei of the pons or medulla. The terminal fibres of these upper neurons are believed by many merely to touch the lower ganglion cells, and by others to be continuous with them.[18] The second or lower set of neurons begins in the large motor cells of the cord and medulla, and extends thence to the peripheral muscles. The voluntary nervous impulse proceeding to the muscles may be interfered with at any point along this long course, with a resulting loss of muscular function. Disturbances of motility may arise, however, from other causes, such as lesions of the muscles, bones and joints, on the one hand, and from lesions of those parts of the nervous apparatus that assist in co-ordinating the movements, or that furnish the will power, on the other.

Some hold that the voluntary motor impulses pass through the cerebellum. However this may be, diseases of the cerebellum unquestionably influence our voluntary movements,[19] independently of their effect upon our

sense of equilibrium. The innervation of muscles is greatly affected by the centripetal impulses that go from them to the brain. These centripetal impulses pass through the cerebellum, so that cerebellar disease at times gives rise to typical ataxia even in the absence of any disturbances of cutaneous sensation. Since the fibres from the cerebellum to the cerebrum undergo decussation, and since the impulses from the cerebrum to the muscles again cross the median line, a unilateral lesion of the cerebellum will interfere with the movements of the muscles on the corresponding side of the body, and this interference may be so marked as to cause a true cerebellar hemiplegia.

If a person is unable to move a certain group of muscles, we speak of it as a paralysis. If the strength of the movement is merely weakened, we speak of it as a paresis. Finally, if the movements are uncertain and irregular, so that a desired movement cannot be accurately carried out, we speak of it as an ataxia.

Paralyses of Psychic Origin.—This class comprises many of the motor disturbances that occur in insane patients, especially during stupor, as well as many of the hysterical paralyses. It hardly lies within the province of this book to discuss the nature of these cases, although the subject is an extremely interesting one. It would be necessary to consider the nature of the will, and the relation that sensations, conceptions and memory bear to it, and then, finally, to take up the manner in which these relations may be disturbed in the various pathological conditions in question.[20]

Such "psychical paralyses" are characterized clinically, mainly by their distribution. We do not will a single muscle to contract, but we will a certain movement to take place, and this movement ordinarily involves the use of numerous muscles. Correspondingly, the paralyses now under consideration do not affect single muscles, but involve whole extremities or the execution of certain movements. For example, a patient may be able to move his legs in every direction without any incoördination, and yet be unable to walk. Or he may be able to execute all ordinary movements with his hand, but be unable to write.

Closely related to these psychic paralyses is the condition known as apraxia,[21] characterized by an inability to per-

form skilled movements with the limbs, though the motor power is intact. The dog becomes apractic after removal of the motor area. As Liepmann and Wilson have shown, the area in man concerned in these skilled movements is located in the first and second convolutions of the left side. The condition is generally ascribed to a loss of motor "concepts," and is of interest particularly because of the insight it gives into the nature of psychic paralyses.

Paralyses from Lesions of the Motor Tracts.—The ganglion cells of the upper motor neurons are situated in the so-called motor area of the cerebral cortex, and the symptoms that result from an injury to this part of the brain depend upon the portion of the motor area that is affected. The axis cylinders of these cells may be injured at any point between their origin and their final termination about the large motor cells of the cord or medulla. The effect of an injury to this motor tract depends both upon which nerve-fibres are injured and upon the severity of the injury. The motor fibres seem to be more susceptible to pressure and stretching than are the sensory. Injuries to this upper tract are caused most commonly by tumors, inflammations and hemorrhages. The ganglion cells in the cord, or their processes in the nerves, may be affected by metallic poisons, such as lead, by the action of micro-organisms or toxins, as in meningitis, myelitis and neuritis, or finally by disturbances of the blood-supply.

Paralyses from Lesions of the Muscles.—Diseases of the muscles naturally interfere with their functional capabilities; as examples of such we may mention the muscular disability which accompanies the dystrophies, trichinosis, polymyositis and the parenchymatous degenerations that follow some acute infectious diseases.

Paralyses from Vascular Disturbances.—Disturbances of the blood-supply to muscles may also interfere with their capabilities. Veterinarians have long known that arterial disease in the legs of horses seriously affects their powers of locomotion. The same is true of man, and the resulting intermittent claudication is apparently much more frequent than is generally supposed.[22] If the arteries supplying an extremity become very narrow, the quantity of blood that reaches this extremity may be sufficient to meet all ordinary needs,

but at the same time it may be insufficient for any extraordinary demands. When the patient walks, therefore, the increased demands of the muscles for fresh blood cannot be supplied, and, after a certain distance, the leg becomes fatigued and painful, so that the patient can walk no farther. If he rests, however, the power gradually returns and the pain leaves his legs, because the supply of blood is again sufficient. These characteristic symptoms of intermittent claudication are usually associated with definite anatomical alterations—usually an obliterating endarteritis—in the vessels of the affected extremities. Not infrequently, these vascular changes eventually lead to gangrene. Apparently a similar intermittent disturbance of function may be caused by a functional, spasmodic narrowing of the arteries from nervous causes. The parallelism between intermittent claudication and angina pectoris is, therefore, rather striking, for both are usually associated with arteriosclerosis, but both may apparently be caused by a nervous spasm of the corresponding arteries.

Myotonia Congenita.—The members of certain families, from youth on, are unable to relax their muscles normally after contraction, because the muscle remains in a sort of tetanus. This rigidity is most pronounced after a period of rest, while, as a rule, it lessens after each repetition of the movement. The muscles themselves are usually quite strong, even more so than normally. We may infer that the cause of the disability is located in the muscle itself, for its reaction to the electric current is abnormal (Erb's myotonic reaction), and its anatomical structure is also considerably altered.[23]

Asthenic Bulbar Paralysis.[24]—This disease, otherwise known as myasthenia gravis pseudo-paralytica, is characterized clinically by the ease with which certain muscles become fatigued after comparatively slight exertion. This fatigue occurs after voluntary use of the muscles, as well as after stimulation by the electric current, but the ease with which the fatigue develops seems to vary from time to time. Certain muscles, especially those supplied from the medulla, tend especially to be affected. This disease involves the motor apparatus, yet the exact point affected is not known, for anatomical investigations have thus far failed to show any lesion.

Disturbances of Coordination.—Before we proceed to the

discussion of the disturbances of coördination,[25] it is necessary to consider the mechanism whereby we normally govern our movements, so that they shall be executed in a precise and exact manner. The consideration of the normal mechanism of coördination presents certain difficulties, however, for we are not certain that it is the same in every case. The adult executes many movements at will, whereas there are others that he learns only by practise. Of the latter, some, such as piano-playing, are learned only by certain individuals, while others, such as walking, speaking and writing, are learned by all men, this being facilitated, doubtlessly, by the fact that our forefathers have practised these movements for generations. There is a gradual transition from the movements that must be learned to the purely voluntary movements, and from these voluntary movements again there is a gradual transition to the purely involuntary movements. To this second transitional class belong those movements of a reflex or automatic type, such as breathing and suckling, that are executed from birth on. As an illustration of the difficulty encountered in attempting to separate these different classes of movements, we may cite the fact that, while swimming must be learned by man, many animals can swim when they first enter the water.

There are, therefore, all grades of transition from the pure reflex movements to the most complex volitional acts. Indeed, the transition occurs many times in the life of a single individual, for movements that were once learned only with the utmost attention and volition are ultimately executed almost unconsciously, merely by willing to do them. At first, these complex acts are carried out under the conscious guidance of all our senses, particularly those of sight, touch, position, etc., but by practice they come to be executed without the individual constituent movements of the act coming to our consciousness.

We know something about the nervous mechanism that underlies these complex practised movements and the more complicated reflexes. These movements may be set in motion voluntarily, or by nervous impulses from the periphery, or, finally, by but little-understood internal chemical changes. Since the resulting movements are varied more or less to suit the occasion, it seems improbable

that they should be guided by a completely developed mechanism lying within the central nervous system. It would appear rather as if they were guided by impulses from the periphery, a supposition which receives strong support from the experiments that have been performed on frogs, dogs and monkeys.[26] If the posterior nerve-roots in these animals be cut—*i.e.*, if the sensory impulses from the periphery be eliminated—not only the complicated reflexes but the more complex practised movements, such as jumping and running, can no longer be carried out as the animal wills, with exactness and precision. Some muscles contract too strongly, others too feebly, and still others at the wrong time, so that the resulting movement, as a whole, loses its precision, and the picture is very similar to that seen in certain nervous diseases that occur in man, especially tabes.

Since an electrical stimulation of the motor region of the cerebral cortex gives rise to movements, not of individual muscles, but of coördinated groups of muscles, we are led to infer that, in the cortex, movements, and not individual muscles, are represented.[27] A further grouping of muscles for the execution of certain movements occurs in the anterior horn cells of the spinal cord and in the root-fibres. It is quite certain, therefore, that a certain degree of coördination is derived from this arrangement of the cells in the motor nervous system, though, as we have seen, this grouping is not sufficient for complex acts. For these we depend more or less upon peripheral sensory impulses. We may or we may not be conscious of these impulses, yet even when we are not conscious of them, they may be utilized by the lower centres in the mechanism of coördination. These two forms of sensation, conscious and unconscious, cannot be strictly separated from each other, for our consciousness of them depends largely upon the attention that we direct to them. Clinical evidence based upon many cases of syringomyelia indicates that in man the loss of sensation proceeding from the skin is in itself insufficient to destroy coördination.

Many varieties of sensation may affect our movements. Of these, we may name the senses of sight and of hearing, those of pressure upon the skin, muscles, tendons and joints, and, finally, the senses of position and of motion.

Some of these are of greater importance than others; and we have seen, for example, that the senses of sight and of hearing alone are inadequate in the monkey and the dog to maintain coördination during such complex movements as jumping and running.

Of the sensations mentioned, the most important in the coördination of voluntary movements are those derived from the tendons, the joints and the eyes.[28] If the two former are affected in the first interphalangeal joints, for example, then even such simple movements as the flexion and extension of the fingers may become ataxic. In addition to these sensations from the joints, tendons and eyes, others from the muscles may also play a considerable rôle in governing our movements.

While the grouping of muscles according to their use in the motor nervous apparatus may, therefore, furnish a rough sort of coördination, this is insufficient for the finer movements. For their execution, centripetal impulses from the periphery are necessary in order to control the time at which the individual muscles shall begin their contractions, the force with which they shall contract and the time during which they shall remain contracted.

After this preliminary discussion of the theory of coördination, it remains to inquire to what extent disturbances of sensation have been actually found in patients who suffer from ataxia, *i.e.*, from an inability to carry out movements in a precise and accurate manner. It is quite certain that ataxia may occur without any demonstrable diminution in the cutaneous senses of pressure, temperature or pain.[29] On the other hand, it has not been shown that ataxia ever occurs independently of all sensory disturbances, and the earlier cases that were believed to prove this were not sufficiently investigated as to the finer losses of sensation in the joints and muscles.[30] Frenkel, in studying one hundred and fifty cases of tabes, failed to find a single instance of ataxia unaccompanied by sensory changes, at least in the joints and muscles.[31] We may say, therefore, that the main cause of tabetic ataxia is a deficiency in the impulses proceeding from the joints and muscles. That this deficiency may be, to a certain extent, compensated for in other ways, is shown by the reliance which ataxic individuals place upon their visual impressions. Possibly the

absent reflexes as well as the diminution in muscular tonus, also play a not inconsiderable part in the motor disturbances of tabetics.[32]

We now come to a consideration of the effect exercised by known disturbances of sensation upon coördination. In other words, do such disturbances necessarily lead to ataxia? Many young, apparently hysterical, persons have been observed who have shown extensive anæsthesias of the skin and of the deeper structures, without, however, exhibiting any true ataxia.[33] When they kept their eyes open, their movements were perfectly normal, which, as we have seen, was not the case when, experimentally, all sensory impulses from an extremity were cut off. If these patients closed their eyes, their voluntary movements were indeed somewhat abnormal, but no true ataxia was present. To my mind, however, it is necessary to be very cautious in our interpretation of these observations, because the sensory disturbances were apparently of an hysterical character. Hysterical disturbances of sensations unquestionably have their seat in the most central part of the nervous system—in the mind itself, so to speak—and even though these patients are not conscious of their sensations, the latter may certainly be utilized by the lower centres for coördination. In no other way can we explain the fact that an hysterical girl, with an absolute insensibility of her hands, is able to execute the most delicate hand-work. Indeed, many hysterical patients do not know that they have anæsthesias, mainly because the latter do not cause any motor disturbances. It seems probable, therefore, that in the cases cited above the ataxia was absent because the patients unconsciously utilized the centripetal impulses coming from the extremities.

Investigations on other forms of complete lack of sensation are so few that it is impossible to render a final verdict concerning the effect that these produce upon coördination. Strümpell, however, has recently published a case in which a complete absence of sensation in the right arm affected movements most seriously. So long as the patient's eyes were kept open, the ataxia was comparatively slight, but, as soon as they were closed, the incoördination became extreme.[34]

We have shown that centripetal sensory impulses are absolutely necessary for a proper

coördination of any complex act. The lesion that produces the incoördination, however, does not necessarily lie in the peripheral tracts, but may be so situated in the central nervous system that it hinders, in some manner, the transmission of impulses across this system, as has been shown in a number of cases.[35] Ataxias may, therefore, be due to different causes, and the resulting clinical picture is not always the same. When we speak of ataxia in general we usually refer to the tabetic type, for that is the most common and the best understood form. In this form, the ataxia is always accompanied by demonstrable sensory changes.

If, from any cause, our movements become more or less incoordinated, then we attempt to compensate for the loss of peripheral control by directing them through the higher centres, very much as does one who is trying for the first time to execute a difficult movement. The movement, thus directed, is usually performed more slowly and less accurately than is one automatically regulated. Indeed, it not infrequently happens that when a normal individual attempts to execute some difficult feat particularly well, *i.e.*, when he watches each individual movement, the act is done particularly badly. This shows the superiority of the automatic regulation over the volitional. A compensation for losses of centripetal control may be developed, however, in another way. When the sensory impulses from the affected extremity are not all shut off, the patient may learn to utilize those that are left to a far greater extent than they were ever used previously, and so to develop a new automatic regulation.

Disturbances of sensation may affect the functions of the body in other ways than by causing ataxia;[36] and here again the loss of certain sensations may be compensated for, to a certain extent, by other sensations, and especially by those that come from the eyes. For this reason, it frequently happens that such disturbances become manifest only when the patient closes his eyes. When the sense of touch in the hands is lost, the patient is unable to grasp objects properly or to gain an idea of the contour of surfaces, unless the eyes follow the movements of the hand. If the senses of position and of motion are diminished, all the finer movements that depend upon the position of the body or of the hand in space are not executed accurately except under ocular

control. The deaf-mute, whose semicircular canals are destroyed, becomes unsteady as soon as his eyes are closed, just as does the ataxic tabetic.

The ataxias, depending upon their anatomical origin, have been classified as peripheral, spinal, pontine, cerebellar and cerebral; and each of these types presents to a certain extent a characteristic clinical complex. This is readily understandable even for those cases due to disturbances of centripetal sensory impulses, for the latter must take paths which vary with the difference in location of the lesion in the above-mentioned forms.

The disturbances of coördination seen in cerebellar lesions deserve a final word.[37] Certain of these disturbances differ in nowise from those of the tabetic. There is this difference, however, that in cerebellar affairs the ataxia becomes less pronounced when the patient lies in bed, for the cerebellum has to do essentially with static control and with the coördination of such movements as walking, standing and running, which are not immediately under voluntary control, but are influenced rather by impulses from such sensory organs as the semicircular canals and the eyes.[38] Lewandowsky[39] has well expressed the function of the cerebellum in this respect in his statement "that the cerebellum governs those phases of our movements not under the influence of the cerebral threshold of consciousness."

The Effect upon Motion of Variations in the Reflexes.—Although the reflexes have been carefully studied, especially in regard to their diagnostic significance, very little attention has been paid to the important influence that they exert upon our voluntary movements, this being due to the effect that they have upon the state of contraction of the muscles. In addition to this they serve to protect the joints from forcible and sudden motions.[40]

It is extremely difficult to estimate the precise injury that is caused by an absence of the tendon reflexes, for such absence is usually associated either with paralysis or with definite sensory changes. The important part played by the latter in the causation of disturbances of movement has already been emphasized—a mechanism which may also be regarded as a reflex. The studies of Sherrington[41] in this field have been extremely elucidative.

When the reflexes are much exaggerated, the tension of the muscles is increased to such a degree that the slightest irritation will call forth a reflex spasm. With every motion, the tendons and ligaments, especially those opposing the movement, are put more or less upon the stretch. This initiates reflex muscular contractions, which tend especially to affect the antagonists of the muscles that are innervated. As a result, all movements become stiff, and in very bad cases even impossible. This reflex innervation of antagonistic muscles may cause such uncertainty of movement that the resulting picture resembles true ataxia, *e.g.*, in multiple sclerosis.

Nervous Disturbances of Urination and Defecation.—The reflex acts of urination and defecation are so far under the control of the will that, up to a certain limit, we can inhibit or initiate them. The nervous impulses running from the brain to the lower centres merely prevent or permit the reflex that is initiated by peripheral sensations.

The reflex centres that control defecation and urination are not situated in the cord, as has been generally supposed, but lie in the sympathetic system.[42] The centripetal impulses that these centres receive from their corresponding organs are, in part, excited by distention of the organ. Yet distention is only one of the factors that initiate the reflex, for we urinate different amounts at different times, and much less when the mucous membrane of the bladder is inflamed, or when the urine is concentrated, highly acid and irritating.

In the new-born infant, urination and defecation are purely reflex phenomena. When the centripetal impulses become sufficiently strong, the reflex mechanism is set in motion and the viscus is emptied. Only through careful training does the child learn to govern these reflexes and gradually to bring them within the normal limits of control.

If the impulses running from the cerebrum to the lower centres be interrupted from any cause, voluntary control over evacuation is lost. For a time after these impulses are cut off, the bladder remains full and continually overflows (incontinence from retention), but gradually it comes to empty itself reflexly at intervals, just as it does during infancy. Since this reflex emptying of the bladder may occur even when the lumbar cord is destroyed, the centre lies outside the cord.

Other nervous lesions cause variable disturbances. For example, a loss of centripetal impulses from the bladder to the reflex centre will lead to a pure retention; while a diminution in these impulses will lead to difficulty in passing urine, to straining and to delay in starting the stream. Lesions of the motor paths may cause similar disturbances, such as slow urination and the retention of urine in consequence of a paresis of the detrusor, and continual dribbling as the result of a weakness of the sphincter. Irritative lesions of the tracts that connect the cerebrum with the reflex centre may cause retention of urine from spasm of the sphincters. Finally, it must be remembered that the external sphincter is a voluntary muscle, and that when it is paralyzed there may result merely an inability to hold the urine when the bladder becomes filled.

The nervous disturbances of defecation appear to be very similar to those of urination.

Pathological Alterations in the Reflexes.—In a pure reflex, the sensory impulse acts immediately upon the motor apparatus without the intervention of the will. The reflex mechanism consists, therefore, of the sensory apparatus, the motor apparatus and the connection between the two. The latter may be situated either in the brain, the spinal cord or the sympathetic system.

The Deep Reflexes.—Those reflexes which arise from the tendons, periosteum or bones, and of which the patellar reflex is the best-known example, traverse the spinal cord or the subcortical portions of the brain. They are subject to many and diverse influences, which may act either directly upon the sensory or motor apparatus, or, more indirectly, may tend to inhibit or to further the transference of the impulse from the sensory to the motor side of the reflex arc.[43]

Even normally there is a great variation in the intensity of the reflexes, not only in different individuals, but in the same individual at different times, the latter being especially true of "nervous" patients. The reflexes tend to be exaggerated during fatigue, as well as in marantic and cachectic conditions. They show considerable variations in the infectious diseases. They usually disappear just before death.

If the reflex arc be broken at any point, whether in the sensory, the motor or central portion, the corresponding reflex is abolished. In the earliest stages of tabes dorsalis, for

example, the knee-jerks may be absent because that part of the cord through which the sensory portion of the reflex must travel has degenerated. Even when the reflex is absent, however, it is possible that the path is not completely blocked, but only to the extent that it inhibits the reflex taking place under ordinary conditions. If such be the case, then a cerebral lesion that would normally increase the reflex may cause the lost one to return. This has been observed in a number of cases.[44]

A disease of the reflex arc, such as a neuritis, at times causes an exaggeration of the corresponding reflex. It is possible that in these cases the inflamed sensory nerves show an increased irritability or conductivity; though it is also possible, as Sternberg believes, that the exaggeration is caused by changes in the reflex centre.

The deep reflexes may be influenced by lesions that lie outside of the reflex apparatus itself. The most important of these are the lesions which interrupt the passage of impulses from the cerebrum, or possibly also from the subcortical centres, down to the lower spinal reflex centres. Injuries of this character are usually followed by an exaggeration of the deep reflexes, and it has been assumed that this results from a blocking of the inhibitory influence which the brain is supposed to exert upon the spinal centres.[45] Yet the correctness of this interpretation may justly be questioned, for numerous observations have established the fact that the patellar reflexes may totally disappear after a complete transverse section of the spinal cord.[46] In some such cases, however, the tendon reflexes have persisted in spite of the transverse lesion; and experiments upon dogs and monkeys have yielded equally conflicting results. In them, a complete section of the cord may be followed either by increased or by diminished reflexes. Immediately after the operation on these animals, the reflexes are usually abolished, but they gradually return after a certain length of time. The primary injury itself may possibly inhibit them for a time, thus causing their early disappearance; but their continued absence in clinical cases cannot be accounted for in this manner. Trendelenburg and Munk, on the basis of their experimental studies, have come to the conclusion that the brain exerts a stimulating, rather than an inhibiting influence, upon the spinal centres, and that the continued absence

of the reflexes observed after section of the cord high up is generally the result of secondary changes.[47]

The Superficial Reflexes.—These are of a more complex character than are the deep reflexes, and their nature is less understood.[48] A relatively slight stimulus applied to the skin or to a mucous membrane will often elicit a relatively strong response, and the resulting movements are usually slower and more under the control of the will than are the deep reflexes. It is quite possible that the nervous path that some of these skin reflexes follow traverses the cerebrum, and that this is the reason why they are so often absent in the very conditions in which the tendon reflexes are exaggerated. Yet this is very questionable and the data at our disposal do not permit us to formulate even an hypothesis as to the nature of the superficial reflexes.

Strychnin Poisoning and Tetanus.—The violent muscular contractions that characterize these conditions are caused by an increased irritability of the cells in the spinal cord. In strychnin poisoning, the convulsions are of a purely reflex nature, *i.e.*, they are excited by sensory impulses from the periphery. In tetanus, some are of this character, while others are due to a primary stimulation of the large motor cells in the cord. These cells, undoubtedly, become abnormally irritable in tetanus, and some remarkable anatomical changes in them have been described.

The brilliant researches of Meyer and Ransom[49] have shown that the tetanus toxin travels from the periphery to the spinal cord through the axis-cylinders of the nerves, and that it cannot attack the cord directly from the blood or lymph. The nerves must first be entered. For example, if tetanus antitoxin be injected into certain nerve-trunks of an animal, and if, at the same time, the toxin be injected into the blood or lymph, the regions corresponding to the nerves that have received the antitoxin are not affected during the ensuing tetanus. When tetanus toxin is injected directly into the spinal cord, the incubation period that elapses before the appearance of symptoms is reduced to about two and a half hours. This demonstrates that the long incubation period usually present in tetanus is due to the time consumed by the toxin in travelling from the periphery to the central structures.

The tetanus toxin first affects the motor cells of the cord in such a way as to irritate them and to cause a tonic spasm of the

corresponding muscles, the spasm not being of a reflex character. The toxin then spreads to neighboring cells, especially to the motor cells lying on the opposite side of the cord, with resulting convulsions in the same muscles as those first affected, but on the opposite side of the body. Still later, when the poison affects the sensory portion of the reflex arc, reflex convulsions occur; yet only those reflexes are increased which pass through the affected parts of the cord.

The sensory nerve-fibres do not seem to be affected by the tetanus toxin under ordinary conditions; yet Meyer and Ransom have shown that if the toxin be injected directly into the posterior nerve-roots, the first symptoms of the poisoning are attacks of violent pain—the so-called tetanus dolorosus.

Tetanus in man differs from that produced experimentally in animals in that the muscles first affected are usually those of the jaw, causing the well-known trismus; whereas, experimentally, the convulsions begin in the muscles that correspond to the point of inoculation.

It is a noteworthy fact that tetanus antitoxin cannot be isolated from the nervous structures it involves; nor does it appear capable of penetrating these structures. This speaks against the assumption that an antitoxin is produced in the cells specifically attacked by the poison. If the latter be prevented from reaching the central nervous system, by cutting the nerves of the extremity into which it is injected, there occurs a marked formation of antitoxin and the establishment of an immunity.[50]

Contractures.—The bones about a joint are not infrequently held in a more or less fixed position. This may be due to a number of causes, such as diseases of the joints, scars in the skin or muscles, and changes in the muscles, either primary or secondary to nervous lesions. Any of these might be termed contractures, though it is customary to restrict the use of the term to those limitations of motion that follow disease of the muscles or of the nerves.[51]

If, for any reason, certain muscles remain shortened over a long period of time, this shortening tends to become permanent, and the movements of the joint are then correspondingly limited. This condition is spoken of as a passive contracture. Of the causes that may lead to such a shortening of the muscles, we may name the maintenance of a certain posture

for a long time. In this manner, a foot-drop is not infrequently produced by the pressure of the bedclothes during a long illness. When certain groups of muscles are weakened or paralyzed, either from disease of the muscles themselves or from disease of their nervous connections, the antagonistic muscles, not meeting with the normal resistance to their action, tend to move the joint into an abnormal position and to hold it there. Whenever the joint has been held in a certain position for a long time, it tends to be fixed in this position both by the development of adhesions about the joint itself and by anatomical alterations in the shortened muscles. Passive contractures have been produced experimentally in monkeys by the extirpation of portions of the cerebral cortex, and by subsequently keeping the animals in such small cages that their movements were very much limited.[52]

In active contractures, the joints are held in an abnormal position by the tonic contraction of certain groups of muscles. Since there is usually an associated increase in the tendon reflexes in these cases, they have been termed by some, spastic contractures. The cause of the muscular spasm which produces the contracture is not always clear, and it may not be the same in all cases. As we have said, the reflexes are usually exaggerated in active contractures, yet not necessarily so, and in some cases they remain unaffected.

When the reflexes are increased, the contractures might possibly be caused by an unequal reflex stimulation of the different groups of muscles about a joint. To my mind, however, this explanation is not an entirely satisfactory one, for it seems very probable that, in many cases, at least, the contractures and the exaggerated reflexes are both due to a common cause.

Mann[53] has given a very plausible explanation of post-hemiplegic contractures. He first calls attention to the fact that these contractures affect especially the muscles that are least paralyzed. In the complicated innervation that directs every voluntary movement, there is apparently not only a stimulation of the muscles that produce the movement, but an inhibition of the antagonistic muscles. A cerebral disease, therefore, will not only paralyze certain muscles, but will, at the same time, diminish the inhibitory

impulses sent to their antagonists. This lack of inhibition would explain the contracture in the antagonistic muscles; and Mann's hypothesis accords very well with the experimental results of H. E. Hering.[54]

At the outset, every complete cerebral paralysis is flaccid, and contractures do not occur until the paralyses of the different muscle-groups affected recede in unequal degree. Centripetal sensory impulses likewise favor the appearance of contractures, whereas the absence of such impulses tend to prevent them (*e.g.,* in tabes). It is evident, therefore, that the mechanism of contracture production is a complex one, depending upon the reflex, and possibly also the direct, stimulation of muscle-groups of antagonistic action, and upon the net result of paralysis and inhibition. That contractures tend to be limited to certain groups of muscles would seem to be due to an unequal stimulation of contiguous cortical areas.

In many cases, irritative processes seem to cause the tonic muscular spasm, though it must be admitted that no very sharp line can be drawn between an irritation and a diminution of inhibitory influences.[55] The valuable studies of Förster[56] have shown how complicated is the mechanism of spastic contractures. A remarkable fact, according to him, is that in the spastic type, no less than in the passive, the long-continued maintenance of a part in one position plays an important rôle. If a muscle has once become shortened by habituation to a certain position, it is more difficult to overcome this after the removal of the cerebral inhibiting influences. And, furthermore, by making use of the observation that voluntary movements also tend to be inhibited, Förster was able to influence even the type of spastic contracture.

A contracture, therefore, is a subcortical reflex representing an increase in the resistance offered by every muscle to forces which tend to lengthen it. The form of the contracture depends upon the position customary to the limbs and also upon the degree of restitution of voluntary movements, which, in turn, differs with the parts affected.

Two views have been advanced as to the cause of the contractures that develop in joint disease. According to the one, the muscle spasm is caused reflexly from the joint, owing to a strong stimulation

of the sensory nerves there. This view is supported by the fact that the tendon reflexes are often increased in these conditions. Personally, however, I am inclined to favor the view that the muscle spasm and peculiar posture assumed by these patients are both the result of a desire to avoid pain; though it must be admitted that this does not explain the increased tendon reflexes.

Hysterical contractures are usually, but not always, associated with exaggerated reflexes. They would appear to be due in part to this exaggeration; in part, perhaps, to a diminution of the inhibitory control normally exercised by the brain over the lower spinal centres.

Motor Irritative Symptoms.—Tremor may be defined as a series of regular oscillatory muscular movements about a fixed axis. The rate of these oscillations, their amplitude and the number of muscles affected, all vary in individual cases. In many conditions, the tremor occurs only during voluntary movements; in others, it is more intense during rest. All forms of tremor cease during sleep. Unfortunately we cannot discuss tremor, because, in our opinion, absolutely nothing is known as to its real cause,[57] and because it is not our purpose to enter into clinical or diagnostic details.

According to Bonhoeffer, the **choreiform movements** that sometimes develop after a hemiplegia are usually caused by lesions of the superior cerebellar peduncles,[58] which would interrupt the centripetal impulses that pass through the cerebellum on their way to the motor region of the cerebral cortex. The muscle tonus in these conditions is usually diminished,[59] a fact which lends some support to the hypothesis that the cerebellar function is affected.

In a variety of pathological conditions, certain voluntary movements are regularly accompanied by other purposeless, so-called **associated movements.**[60] As we have already stated, the innervation for a voluntary movement is extremely complex, impulses being sent to a great number of muscles. The muscular contractions that would result from all these motor impulses are, however, controlled by other impulses that come in from the periphery. If this peripheral control be lost, it is possible that certain acts should be accompanied by extra, purposeless movements which would be suppressed in the normal individual. The

associated movements that may occur in tabes dorsalis are, therefore, related in a way to the ataxia, for both depend upon a loss of centripetal peripheral control.

Convulsions may be of the clonic type, *i.e.*, the muscles are alternately contracted and relaxed with corresponding movements of different parts of the body; or they may be of the tonic type, *i.e.*, the contraction is continuous and the parts affected simply become rigid. Finally, the two forms of convulsions, tonic and clonic, may alternate with each other.

Convulsions may be caused either by stimulation of the motor tracts or nerve-cells. For example, diseases of the cervical or dorsal cord may cause convulsive movements in the legs owing to an irritation of the motor tracts; lesions of the internal capsule may cause convulsions in the opposite half of the body; disease of the cerebral cortex in the corresponding extremity, etc. It would appear, however, that the stimulation of the cerebral cortex is more likely to produce convulsions than is stimulation of any other part of the motor apparatus.

The paradigm of cortical convulsions is the so-called **Jacksonian epilepsy,** which is characterized by its limitation, at the outset, to certain groups of muscles, whence it spreads, as a rule, to the entire body. The convulsions are generally followed by a more or less transitory paralysis of the affected muscles. The order of progression of the convulsions corresponds to the arrangement of the cortical centres governing the particular groups of muscles.

Many poisons produce convulsions, some of which, such as the uræmic and diabetic poisons, are formed within the body during pathological processes. It is impossible to say, however, upon which part of the central nervous system these poisonous substances act, though in all probability it is the cortex.

Epilepsy[61] is apparently due to an excessive irritability of the central nervous structures. The convulsions themselves may be precipitated by sensory impulses from some part of the surface of the body, but more frequently they come on spontaneously, or, at least, without any discoverable cause. The attack is often preceded by certain characteristic psychic or bodily warnings (aura). The patient then becomes unconscious and general convulsions occur, which are at first tonic and later clonic in character. It is possible to induce tonic as well as clonic

convulsions in animals by stimulating various parts of the brain, such as the medulla, the pons and the sensory and motor regions of the cortex. Of these convulsions, no type presents so great a similarity to the attacks of epilepsy as does that which follows stimulation of the cerebral cortex. The latter may be either fully developed or rudimentary in type, and it often continues after the stimulation has ceased. The similarity that exists between the convulsions of epilepsy and those that follow stimulation of the cerebral cortex favors the view that epilepsy is of cortical origin. This view is supported furthermore by certain clinical facts, such as the frequency of rudimentary epileptic attacks, the associated unconsciousness, the spread of the convulsions in accordance with the cortical representation of muscles and the frequent occurrence of sensory aura.

Disturbances of Sensation.—The pathology of sensation is so intimately associated with the mind itself that our consideration of this subject will necessarily be limited, for, as we have already said, we do not purpose discussing psychic changes. It will be necessary to limit our discussion in still another way, *viz.*, by omitting the special senses of sight and hearing, for these subjects require so much special knowledge that we cannot do justice to them.

Disturbances of sensation may be either irritative or paralytic in character, and the sensory mechanism may be injured at any point from its beginning in an end organ at the periphery to its termination in the central perceptive part of the cerebrum. If the peripheral sense organ is injured, if conduction of the impulse through the nerve or cord be interrupted, or if, finally, the connections in the brain be thrown out of function, the sensation will be either distorted in some manner, or it will not be perceived at all.

In certain spinal or peripheral diseases, the sensations are, indeed, perceived, but they travel at a slower rate than normal. This occurs most frequently in tabes dorsalis and affects oftenest the cutaneous sensation of pain. We do not know exactly how this delayed sensation is caused.

When a certain injurious agent affects at one time a number of nerve-fibres of different functions, the sensory fibres usually resist the injury better than do the motor. Under such circumstances, the motor fibres may be paralyzed, while the sensory

fibres are merely irritated and cause pain. This combination of symptoms is seen especially from pressure upon the spinal cord, producing the characteristic picture of paraplegia dolorosa.

Our whole knowledge of the external world comes to us through centripetal nervous impulses, all the functions of our bodies being more or less affected by them. Thus, the sensations of light, sound and temperature influence metabolism, muscular activity and respiration. When one form of sensation is lost, the others become more acute because more attention is directed to them, the best known example of this being the acute sense of touch that is developed in blind individuals.

The Cutaneous Sensations.—The nerves of pressure, pain, heat and cold, each possess definite and characteristic endings in the skin.[62] These delicately constructed end-organs are without doubt injured in some skin diseases, although, so far as I know, no thorough study of such injuries has yet been made. Diseases of the nerves or of the central apparatus may also affect the cutaneous sensations, and any one of the latter may be disturbed without the others being affected. Such "partial anæsthesias" may result from disease either of the nerves or of the central nervous system, but they are especially frequent in tabes and in syringomyelia. The occurrence of such partial anæsthesias is of great practical and theoretical interest, for it implies that special nerves exist for each of the cutaneous sensations. In particular, it tends to prove that pain is due to the stimulation of special pain fibres, and not to the overstimulation of other varieties of fibres. The physiological observation that certain points in the skin are sensitive to pain alone and others to pressure alone, likewise supports this view. It must be noted, however, that even so experienced an investigator as Goldscheider[63] denies the existence of special nerves for pain.

Lesions of the peripheral nerves may also affect the different skin sensations to different degrees, and in this manner give rise to partial anæsthesias; but the most pronounced instances of this condition are usually observed in diseases of the spinal cord. The fibres that transmit the various forms of cutaneous sensation apparently run in different parts of the cord, with the result that a limited lesion may block some of them and leave others intact.

The path pursued by the sensory fibres in the central nervous system is an extremely complex one. A portion of the fibres that carry impulses to the brain cross by way of the anterior commissure to the opposite side of the cord shortly after they enter it. This is the explanation of the Brown-Séquard symptom-complex. If one-half of the spinal cord be destroyed, the muscles on that side below the level of the lesion will be paralyzed, with an associated loss of the sense of position. The cutaneous sensations that are interrupted, however, are those that come from the opposite side of the body below the lesion.

When the sensory tracts reach the brain, they connect with various reflex and automatic centres, some finally terminating in the cerebral cortex, apparently in the neighborhood of the motor areas that govern the movements of corresponding parts of the body. For this reason, lesions of the cortical motor area usually produce a diminution, though not a complete loss, of sensation in those parts of the body that correspond to the paralysis. So far as sight and hearing are concerned, we know that a sensation may be perceived without its meaning being recognized (soul blindness); thus a patient may hear the ringing of a bell, but he unable to tell what causes the sound.

The sensory disturbances due to diseases of the peripheral nerves demand a special word. The observation that severance of a cutaneous nerve does not render the area supplied by that nerve entirely anæsthetic has been explained on the basis of nerve anastomoses and the overlapping of nerve supplies. Head and his co-workers[64] have elaborated another theory, *viz.*, that cutaneous sensation is carried by three distinct types of nerve fibres, exclusive of those for the feeling of cold, heat and pain. Those for deep sensibility course with the motor fibres, entering the anterior horns, traversing the cord to the posterior roots and thence entering the spinal tracts. Through the medium of these fibres it is assumed that we experience the sensations of pressure, pain and movement of the deeper structures. Superficial sensation, according to Head, falls into two classes, which he terms "epicritical" and "protopathic," the first conveying the finer impulses, the latter the coarser. The epicritical fibres are said to correspond approximately to the anatomical distribution

of a given nerve, and to regenerate much more slowly than do the protopathic fibres. This hypothesis has not been unchallenged.[65]

Every sensation produces at the same time a more or less definite impression of the place whence the sensation has come. In the case of the eyes and skin, this localization is very accurate; in the case of the mucous membrane near the outside of the body it is somewhat less accurate; while in the case of the deeper mucous membranes and the organs within the body, it is inaccurate and entirely unreliable. In certain nervous lesions, especially in those about the optic thalami, the cutaneous sensations are perceived, but the ability to localize them is more or less lost. Curiously enough, this sense of locality is well preserved in cortical lesions.[66] Observers are not agreed as to whether this sensory anomaly is due chiefly to a loss of the sense of movement, or of cutaneous sensation; at any rate, it is most marked when both are involved.

The Orientation of Our Bodies in Space.[67]—We derive information as to the position of our bodies in space from a number of sources. Our eyes aid us by means of the images upon the retinæ and by their motion within the orbits; the internal ear enables us to estimate changes in the rate of direction of our movements; and other more or less valuable data are derived from the muscles, tendons, bones, joints, skin, etc. Even though we are not conscious of these various sensations, they all influence to some extent the conception that we have as to our position in space.

Certain of these sensations may be lost without much effect upon our powers of orientation, for the reason that other sensations compensate for the lost ones.[68] The blind man moves about a room with great precision so long as he can use his sense of touch; and the deaf-mute hardly seems to be affected by the loss of his internal ears. It is an interesting fact, however, that deaf-mutes do show a diminished power of orientation, and that they behave quite differently from normal individuals when they are turned about rapidly.[69] The tabetic who has lost certain of the sensory impulses coming from his legs depends very much upon his visual impressions, and if these be taken away from him by closing his eyes he will often immediately fall to the ground. We see, therefore, that various disorders of the peripheral sensory apparatus will disturb the sense of

our position in space. The same effect may also result from lesions of the central mechanism in the brain—above all, from lesions of the cerebellum.

Dizziness.[70]—We do not mean by dizziness a partial, transitory loss of consciousness, but a feeling that we are unable to control our equilibrium. This feeling usually results from an inability on the part of the central apparatus to harmonize the various centripetal impulses that come to it.[71] For example, if certain ocular muscles are paralyzed, the images of an object looked at do not fall upon corresponding points of the two retinæ as they normally should, and consequently the impressions derived from the two eyes will not correspond to each other. This causes a sensation of dizziness, which may usually be relieved if the impressions derived from the offending eye are excluded by closing it. Diseases of the semicircular canals, of the sacculus or utriculus, or of their central nervous connections in the cerebellum, are especially likely to cause dizziness, which is most marked when the disease is limited to one side.

In aural vertigo (**Menière's disease**), the dizziness is usually associated with disturbances of hearing.[72] The cochlear branch of the auditory nerve transmits sensations of sound; whereas the vestibular branch, proceeding from the vestibule and the semicircular canals, carries impulses that are caused by changes in the rate or direction of our movements. The symptom of dizziness in aural vertigo undoubtedly results from disturbances in the impulses carried by the vestibular nerve. The associated anomalies of hearing are easily understood when we consider the close proximity of the two nerves and of their end organs. In many cases, the sensation of dizziness will disappear if the patient remain perfectly quiet, while in others they are constantly present even though the patient be still, and under such circumstances they are most harassing.

The dizziness of aural vertigo is probably due to an irritation of the vestibular nerve, or of its connections, rather than to a mere lack of function. The patient becomes dizzy because the impressions received from this source do not coincide with those received from other parts of the body. That the dizziness in these cases is not due to a mere lack of sensation from the internal

ear is rendered probable by the fact that the typical symptoms of aural vertigo are rarely seen in those deaf-mutes in whom the internal ear is entirely functionless.

Aural vertigo, as well as cerebellar vertigo, is frequently associated with other symptoms, such as vomiting, uncertainty in the voluntary muscular movements, especially in walking, and peculiar movements of the eyes. At present, however, it is impossible to explain these associated symptoms very satisfactorily.

The sensation of dizziness may also be produced by many other causes, such as alcoholic intoxication, cerebral pressure, anæmia and circulatory disturbances; yet the exact mode of its causation in these conditions is not known.

Hyperalgesia.—Increased sensitiveness to painful stimuli that are applied to the skin has been observed in various diseases of the cord and of the more central endings of the sensory tracts. The transition from the normal to the pathological, however, is here a very gradual one, and individuals of a "sensitive" nature are certainly more susceptible to pain than are those of a phlegmatic type. The hypersensitiveness of hysterical patients is probably of this perceptive character. Peripheral abnormalities rarely give rise to hyperalgesia, although a neuritis will sometimes do so. Occasionally, as in cord lesions, hyperalgesia may result from the summation of many stimuli, no one of which in itself is sufficient to give rise to a painful sensation.

Irritative Sensory Symptoms.—These differ from the preceding in that the pain results not from hypersensitiveness to normal stimuli, but from a pathological irritation of the sensory mechanism.

Itching is usually caused by an irritation of the sensory organs in the skin, though sometimes, as in multiple sclerosis, it may result from lesions of the conducting apparatus. It accompanies most cutaneous diseases, but, for some unknown reason, it tends to be absent in certain lesions, such as those produced by syphilis. Not infrequently, itching is present when no cutaneous changes can be demonstrated, as, for example, in jaundice and diabetes. It is possible that in these cases the central apparatus is directly irritated. On the other hand, paræsthesias, such as numbness and tickling, rarely accompany cutaneous diseases, but are caused usually by nerve or cord lesions. They have also been observed in the extremity that corresponded to

a point of softening in the sensory sphere of the cerebral cortex. They seem, therefore, to be caused by an irritation of the sensory tracts.

Abnormal sensations of heat and cold are sometimes experienced, but it is often difficult to distinguish these from the accompanying sense of pain.

In our opinion, pain is normally caused by the stimulation of special pain fibres or sensory end organs. Heavy pressure, for example, will deform the skin and so stimulate the pain points. Pain also results from various inflammations and degenerations of the nerves, such as may be caused by alcohol, arsenic, malaria, etc. The nerves may also cause pain even when no demonstrable lesion is present, as happens in the neuralgias.

It is remarkable that pathological processes within the central nervous system itself rarely produce much pain, so long as the peripheral nerves, the posterior roots and the meninges remain unaffected. Surgeons and physiologists have frequently demonstrated that the brain itself is practically insensible; and although it cannot be denied that the pain fibres may be stimulated within the central nervous system,[73] yet the general fact remains that such a stimulation is not easily brought about.

Many hysterical pains are probably of a central, "psychic" nature, but these are not related in any way to organic lesions of the cerebral cortex.

The Influence of the Nervous System upon the Tissue Nutrition.—The nutrition of a tissue depends primarily upon the activities of its individual cells. It is, indeed, necessary that food material should be supplied to it from the blood in sufficient quantities, yet this food supply alone does not stimulate the growth of the cell. That stimulus must come from the parenchyma itself.

The exact part that the nervous system plays in this process is not at all clear. Beyond question, it exerts a very important influence upon the nutrition of certain tissues. Is this influence, however, due merely to the fact that the cells do not functionate properly without nervous impulses, or do the nerves contain some specific, nutritional, "trophic" fibres?

The Effect of Separating a Nerve-Fibre from Its Cell.—The nerve-fibres degenerate if they are separated from their ganglion cells, or if these cells are destroyed. This is explained, according

to the neuron theory, on the assumption that the nerve-fibre, a long process of the ganglionic cell, dies when it is separated from its mother cell.

It is not our intention to consider the validity of the neuron theory nor the recent arguments advanced both in favor and against it. The cells and their axis-cylinders undoubtedly have an intimate histological relationship. On the other hand, we can no longer subscribe to the neuron theory in its original form,[74] for there can be no question of the important part played by nervous structures other than the ganglion cells and axones, *e.g.*, the neurofibrillæ. (The neuron theory, though in its entirety perhaps not unassailable, seems to be the most acceptable at our disposal, and is held by the majority of physiologists. Especially indicative of the fact that the nerve-cells are concerned not merely with the nutrition of the conducting fibres, but themselves take part in the transmission of impulses, are the brilliant researches of Harrison[75] who was able to show *in vitro* that the growth of the axis-cylinder occurs when all other nervous structures are eliminated but the nerve-cells whence they arise.—Ed.)

Some indeed assert that the mere separation of the fibre from the cell, or rather, the cessation of the influence that the cell exerts over the fibre, is not the cause of the degeneration, but that the latter is due directly to the traumatism of the operation.[76] It is possible, for example, experimentally, to interrupt the transmission of nervous impulses through a fibre for a very long time without having any degeneration take place; but although the ordinary nervous impulses were interrupted in such a case, we cannot be sure that the nutritional impulses were likewise affected.

Even though the nerve-fibre is a part of the ganglion cell, the two must be, to a certain extent, independent of each other, for the fibres seem to be relatively much more susceptible to the action of certain toxins. The neuritis that follows the circulation of these toxins in the blood apparently occurs either because the fibres contain elements for which the toxins show a special affinity, or because the fibres are so remote from their nutritional centres, the cells. The fact that medullated nerve-fibres pursue a different course of regeneration than do the non-medullated, suggests that the medullary sheath plays an important part in this selective action of toxins upon the nerve-fibres. In many cases the nerves

are capable of exchanging material with their surroundings, as is evidenced especially by the fact that the tetanus toxin travels from the periphery to the cord through the axis cylinders. Possibly the toxins of other infectious diseases pursue this same course, and if this were so it might explain the special susceptibility of the nerve-fibres to the toxins of infectious processes.

In some instances, as in lead poisoning, different portions of the nerve-cell may be affected, and consequently, widely different nervous symptoms may be produced. Certain of the systemic diseases of the spinal cord show various transitions into one another; and it is easy to conceive, for example, that the same cause might produce in one person a progressive muscular atrophy, in another, an amyotrophic lateral sclerosis, and in a third, a true spastic paraplegia, depending upon whether the pyramidal tracts or the motor cells of the anterior horns were more especially affected.

When a ganglion cell is separated from its peripheral neuron, the former also undergoes certain changes,[77] which reach their height in about eighteen days. After this, a portion of the injured cells may be restored to their normal condition. If the cell continues to be functionless, however, for the reason that the peripheral nerve cannot regenerate, then it gradually undergoes atrophy. This happens, for example, after amputations; and the younger the individual the greater is the cell destruction. These facts are of considerable theoretical interest, for they show that the normal existence of a ganglion cell depends largely upon its ability to exercise its function. Degeneration occurs in the sensory cells because they receive no impulses from the periphery, and in the motor cells when they no longer receive those indirect stimuli from the muscles and other tissues which normally play so great a part in the regulation of their activities.

It is apparent, therefore, that our knowledge of the factors concerned in degeneration and regeneration of nervous elements is by no means complete, even though we regard the neuron as embracing all of the structures concerned in the functional activities of the nervous system—a view, incidentally, which is undoubtedly too narrow. The interpretative difficulties are only increased, however, if we go beyond the neuron and attribute special properties to other structures, such as the fibrillæ, etc.

Nutritional Disturbances in the Muscles.—When the muscles are separated from the spinal cells that innervate them, they degenerate. The degenerative changes consist mainly in alterations of their chemical composition[78] and of their electrical irritability. Prominent among the chemical changes, according to Rumpf, is a marked diminution in the potassium, and a considerable increase in the sodium, salts. In addition to these, a simple reduction of their contractile substance without degenerative changes takes place.[79] The reduction of the quantity of protoplasm is caused by the inactivity, and is, therefore, an atrophy from disuse. The microscopical signs of degeneration, such as the granular and waxy degenerations, are not due to the separation of the muscles from the cord, but to some associated action of toxic substances.

Changes in the Electrical Irritability of Muscles.[80]—After a muscle has been separated from its ganglion cells for a certain time, it responds abnormally to the electric current. These changes constitute the so-called reaction of degeneration. It will no longer contract when its nerve is stimulated in any manner by the electric current, nor will it contract when it is itself directly stimulated by an ordinary interrupted current. Even the healthy muscle does not contract if very high frequency currents are applied to it, so that the loss of irritability that the degenerated muscle shows toward an interrupted current is merely one of degree. It is an exaggeration of the normal. In this respect, the degenerated muscle behaves like a smooth muscle, for the latter also usually fails to respond to an interrupted current.

The muscle that is separated from its ganglion cells will, however, respond for a long time to interruptions of the galvanic current; and it will, indeed, respond to a much weaker current than does the normal muscle. The contraction produced by this current is not a prompt and short one, as is the case with the normal muscle, but is very slow and easily passes into tetanus. A slow contraction of this kind is also seen in the smooth muscle, in the fatigued striated muscle, in the muscle subjected to cooling by carbon dioxide[81] and in certain intoxications and cachectic conditions. The contraction curve of the cooled muscle—especially the gradual ascent—may so closely resemble that of the reaction of partial degeneration as to be indistinguishable at

times, even by capable observers. In certain fundamental particulars, therefore, the fatigued or cooled muscle reacts exactly as does the degenerated.

The degenerated muscle, instead of responding more strongly to a closure of the current when the cathode is placed upon it, frequently contracts more strongly to the anodal closure. It has been commonly assumed that this change is due to some fundamental alteration in its protoplasm, whereby it is rendered more irritable to the anodal closure; yet such does not seem to be the case. The muscle conducts the current, and, when the cathode is placed over its centre, for example, the current enters at the end and this receives an anodal stimulation. In the normal muscle the cathode causes a stronger contraction, because it is placed over the point of greatest irritability, *i.e.*, the entrance of the nerve into the muscle. The centre of the degenerated muscle, however, early loses its irritability, and the extremities become the most irritable parts. When, therefore, an electric pole is placed over the centre of a degenerated muscle, and the current is closed, the end of the muscle receives the main stimulation. For this reason the maximal contraction is obtained when the anode is placed on the muscle, for the cathodal stimulus then acts upon its more irritable extremity.[82] If the degenerated sartorius muscle of a frog be isolated and stimulated, it shows no diminution in its irritability to the cathodal, as compared with the anodal, closure.[83]

More recently the attempt has been made to explain these phenomena on a physico-chemical basis.[84] According to Nernst, the contraction of a healthy muscle is due to an accumulation of electrolytes at the cathode. Reiss, using frog-muscle preparations freed from nervous connections, has found that in degenerative conditions the normal cathodal accumulation is replaced by an anodal, *i.e.*, the electrolytes gather about the anode instead of the cathode when the circuit is closed.[85] Though it is true, as pointed out above, that degenerated muscle exhibits an altered salt content,[86] and that this alteration might account for such a reversal in the response to cathodal and anodal closure, yet there exist a number of objections, both interpretative and technical to the Reiss hypothesis.[87]

In certain instances, such as in trichinosis and some muscular

dystrophies, the reaction of degeneration has been present without demonstrable lesions of the nerves. At the present time, however, these cases cannot be accepted as proof that the reaction of degeneration may occur independently of nervous lesions, for it is almost impossible to exclude changes in the finer nerve filaments. Nor have the observations on cases of this kind taken into account the pronounced effect of temperature variations, such as cooling, to which attention has already been called. Against Strümpell's view that the reaction of degeneration is simply the response of a nerveless muscle speaks the fact that curarized muscle does not exhibit this phenomenon.

When a motor nerve is injured, but not entirely destroyed, electrical changes of a less marked degree take place in the muscles —the so-called partial reaction of degeneration.

Atrophy from Cerebral Lesions.—When muscles are paralyzed from a cerebral lesion, the resulting atrophy develops more gradually and is of slighter extent than that which follows the division of a peripheral nerve, and it is, furthermore, unaccompanied by the reaction of degeneration. In such cerebral paralyses, only one form of stimulation—the voluntary—is shut off from the paralyzed muscle. The reflex and automatic stimulations from the lower centres continue to act upon it. The paralyzed muscles frequently do contract from reflex stimulation, and even when they do not apparently do so, they still maintain their muscular tonus. The paralyzed muscle that retains a connection with its ganglion cells exhibits a more active metabolism than the paralyzed muscle that is separated from these cells, a further proof that the former maintains a certain amount of activity.

In certain instances, especially in the young, cortical lesions have been followed by marked changes in the lower neurons and by a rapid atrophy of the muscles.[88] The electrical reaction in these cases is usually qualitatively normal, although, in a few, the slow contraction of degeneration has been present. The upper neurons apparently exercise some influence upon the peripheral neurons, and when this is cut off in early life, the latter may degenerate.[89]

Muscular Atrophy from Diseases of the Joints.[90]—The atrophies about diseased joints often develop more rapidly and are more severe than those which are caused by cerebral lesions. As a rule, they do not affect equally all muscles about the joint,

but tend especially to injure the extensors. The severity of the muscular atrophy bears no definite relation to the intensity or variety of the joint lesion. The electrical irritability of the muscle is usually reduced, but no typical reaction of degeneration is present. This form of atrophy differs, therefore, from that caused by cerebral lesions in its intensity and in the rapidity with which it develops, and from that caused by nerve-lesions in the absence of a reaction of degeneration.

Various attempts have been made to explain these muscular atrophies about diseased joints. The French, following Charcot's lead, have generally considered that the nervous impulses sent from the joint to the cord influence the motor cells there, and that a disturbance of the impulses from these cells causes the atrophy. The Germans, following Strümpell, have been more inclined to attribute these muscular atrophies to an extension of the disease by contiguity from the joint to the muscle, though it must be admitted that, experimentally, at least, no inflammation of the muscle is necessarily present, and that the muscles atrophy throughout their entire length, and not merely in the neighborhood of the joint. Finally, attention has been called to the fact that the most seriously affected muscles are precisely those whose movements are most limited by the joint disease, so that the atrophy is probably caused, in part at least, by disuse.[61]

The Muscular Dystrophies.—This disease-group, which exhibits a distinct hereditary and family tendency, is characterized by a very gradual atrophy of certain muscles. It usually begins in childhood or early youth. Several types have been described, but it seems very probable that they are all but different variations of the same disease. Anatomically, we find many atrophied fibres, and, in addition to these, usually a number of thickened fibres, which may, indeed, be so numerous that the muscle as a whole appears to be hypertrophied. The adipose tissue between the muscle fibres is sometimes so increased in amount as to produce a large, weak muscle, the so-called pseudohypertrophy. In the great majority of these cases, no reaction of degeneration is present, while in the few instances in which it has been found, it is extremely difficult to exclude some slight involvement of the finer nerve-filaments,

or the effect of cooling. Even the presence of changes in the spinal cord, such as have been described,[92] do not permit us to assume that this disease is of central origin; for, as we have seen, an atrophy of the ganglion cells may follow a primary peripheral condition, such as an amputation. In a few cases, classified among the dystrophies, some complication may have caused the cord lesion.

Nutritional Disturbances of Nervous Origin in the Bones and Joints.—After an acute anterior poliomyelitis in children, the bones of the paralyzed extremities frequently fail to develop to their normal size; whereas, after the cerebral infantile palsies, their growth is rarely much affected. In the former cases, the absence of the varying pressures and movements to which the bones are normally subjected, may diminish their blood-supply and so retard their development; but it is possible, on the other hand, that this retardation is due to an absence of specific, trophic influences. In adults, nutritional changes in the bones rarely result from diseases of the peripheral motor neurons alone.

In a variety of other nervous diseases, especially in syringomyelia and tabes, as well as in certain peripheral lesions, very remarkable nutritional disturbances take place in the bones and joints.[93] The anatomical changes in the joints often resemble those of arthritis deformans, but they differ from these in certain particulars, especially in the more abundant effusion, the greater destruction of the joint, the rapid course and the frequent absence of all pain. In a certain proportion of these cases, the lesions are, undoubtedly, due to an absence of the sense of temperature and pain. I have myself seen a man with syringomyelia who, while at work, frequently injured himself from grasping live coals, who paid no attention to his wounds on account of the absence of pain, and who eventually developed the most pronounced deformities in his bones and joints. Such observations are not infrequent. In locomotor ataxia, also, injuries are frequently overlooked on account of the loss of sensation in the joints and muscles. In spite of these observations, however, the opinion of the authorities is now gradually turning toward that of Charcot, who held that the arthropathies are caused, in many instances at least, by a loss of trophic impulses from the cord. Patients

have been observed in whom the most severe joint destructions have followed within a few days after nervous lesions, without any demonstrable mechanical injury.

In some nervous diseases the bones are abnormally thin, and they may be fractured from very slight causes, or even, to all appearances, spontaneously. Various cord changes have been found in such patients,[94] and in some cases a neuritis has been present. Although a number of other explanations has been offered for this abnormally brittle character of the bones, it seems probable that a lack of trophic influences is the cause in many cases. In others, local changes, especially syphilitic, may be present in the bone. Nor must the chemical action of the correlated internal secretions be overlooked.

The Influence of Nervous Diseases upon the Skin.—It is well known that those parts of the skin which are exposed to continued pressure tend in time to become reddened and swollen, and eventually to die. Such ulcerations, of which bed-sores furnish the most familiar examples, may develop under a great variety of conditions, depending mainly upon the nutrition of the cells and the constancy of the pressure applied. They are seen especially in patients with nervous, infectious or metabolic diseases, who have lain for a long time in one position. In a certain proportion of the nervous cases—for these are the ones that especially interest us—the ulceration is favored by the cutaneous anæsthesia, and by the soiling of the skin with urine and fæces, owing to a paralysis of the bladder and rectum. As evidence of the importance of these factors, we may instance the brilliant results that follow the proper care of this class of patients. While we must admit, therefore, that the anæsthesia and lack of cleanliness are important factors in the causation of these ulcerations, yet, in my opinion, they are not the only causes that are present, for at times the ulcers develop very rapidly even when there is no loss of sensation and no loss of bladder or rectal control. In this last class of cases, trophic disturbances certainly play an important rôle. To what extent such trophic disturbances and to what extent the other factors enter into the causation of the ordinary bed-sores that develop during nervous diseases can only be determined by modern observations during a proper care of the patient.

Herpes Zoster.—This remarkable eruption is associated with

disturbances of the peripheral nerves, usually an inflammation of the sensory ganglion itself or of the nerve. (Rosenow,[95] in a recent study, has been able to produce in rabbits and other animals herpes of the skin, tongue or lips, and lesions in the corresponding spinal ganglion by the intravenous injection of emulsions of extirpated tonsils, of mixed and pure streptococcal cultures from tonsils or pyorrhœal pockets, and of streptococci in pure culture from the spinal fluid. In the affected ganglion were found, as a rule, hemorrhages and round-cell infiltrations, and Gram positive diplococci and short chains.—Ed.)

The mere loss of a sensory nerve or ganglion does not cause nutritional disturbances in the skin or mucous membranes. This has been sufficiently proved by the results of extirpation of the Gasserian ganglion for facial neuralgia.[96] After such extirpations, trophic disturbances of the skin over the face or of the mucous membrane of the nose or mouth do not occur. Even the cornea and conjunctiva remain intact if protected from direct injury. The keratitis observed in animals after excision of the trigeminus is due to the dry condition of the eye.[97] Since in man the eye may be kept moist by proper precautions, no keratitis necessarily results after the nerve is severed.

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